Animal models of human behavior

Jonathan Flint


Small drink


A drink this size

Reasons why human genetics does not work

Reasons why human genetics does not work: not enough samples

Go get 200 families

Reasons why human genetics does not work: not enough samples

Go get 20,000 families

Power Of Linkage To Detect A Moderate Genetic Effect

Genotypic Risk Ratio	Frequency of disease allele	No of Families Required
4	0.01	**4,200**
	0.50	**300**

Genotypic Risk Ratio: the increased chance that an individual with a particular genotype has the disease

Risch and Merikangas, Science, 273: 1516, 1996

Power Of Linkage To Detect A Moderate Genetic Effect

Genotypic Risk Ratio	Frequency of disease allele	No of Families Required
4	0.01	**4,200**
	0.50	**300**
2	0.01	**296,700**
	0.50	**2,500**
1.5	0.01	**4,620,800**
	0.50	**18,000**

Genotypic Risk Ratio: the increased chance that an individual with a particular genotype has the disease

Risch and Merikangas, Science, 273: 1516, 1996

The common PPARγ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes

David Altshuler[1,2,3*], Joel N. Hirschhorn[1,3,4*], Mia Klannemark[5], Cecilia M. Lindgren[1,5], Marie-Claude Vohl[6], James Nemesh[1], Charles R. Lane[1], Stephen F. Schaffner[1], Stacey Bolk[1], Carl Brewer[6], Tiinamaija Tuomi[5,7], Daniel Gaudet[8], Thomas J. Hudson[1,6], Mark Daly[1], Leif Groop[5] & Eric S. Lander[1,9]

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type 2 diabetes. By analysing over 3,000 individuals, we found a modest (1.25-fold) but significant (*P*=0.002) increase in diabetes risk associated with the more common proline allele (~85% frequency). Moreover, our results resolve a controversy about common variation in PPARγ. An initial study found a threefold effect[12], but four of five subsequent publications[18–22] failed to confirm the association. All six studies are consistent with the odds ratio we describe. The data

The common PPARγ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes

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analysis: in a case such as Pro12Ala, the risk allele will typically be transmitted from both parents, requiring a genome scan of roughly 3 million sib pairs to obtain a lod score of 3. Thus, the genetic dissection of common diseases will surely involve association studies performed on large population samples.

Table 2 | **Approximate sample sizes needed to detect a significantly increased allelic odds ratio***

Disease allele frequency	Marker allele frequency	Allelic odds ratio of disease gene					
		3.0		2.0		1.3	
		No. cases (= no. controls)	No. cases: no. controls (= 1:4)	No. cases (= no. controls)	No. cases: no. controls (= 1:4)	No. cases (= no. controls)	No. cases: no. controls (= 1:4)
0.05	0.05	360	210:840	1110	650:2600	9500	5600:22400
	0.1	600	350:1400	2000	1200:4800	19000	11500:46000
	0.2	1170	700:2800	4150	2500:10000	40000	25000:100000
	0.3	1900	1200:4800	6800	4300:13200	70000	43000:172000
	0.5	4200	2700:10800	15000	9500:38000	160000	100000:400000
0.2	0.05	710	420:1680	1900	1090:4360	14000	8500:34000
	0.1	350	200:800	900	500:2000	6600	4400:13600
	0.2	150	85:340	360	220:880	2900	1750:7000
	0.3	210	130:520	530	360:1440	4800	3000:12000
	0.5	430	270:1080	1250	800:3200	11000	6950:27800
0.5	0.05	3150	1870:7480	6800	4000:16000	40000	25000:100000
	0.1	1500	900:3600	3200	2000:8000	19000	12000:48000
	0.2	640	390:1560	1350	850:3400	8500	5300:21200
	0.3	360	220:880	800	500:2000	5000	3100:12400
	0.5	140	90:360	320	200:800	2100	1300:5200

*Using diallelic markers with varying allele frequency and allowing linkage disequilibrium between marker and disease allele down to $D' = 0.7$, odds ratio (power = 80%; $\alpha = 0.001$).

Zondervan and Cardon, Nat Rev Genet 5: 89, 2004

Go sample a continent

Reasons why human genetics does not work

- There are not enough people on the planet

Reasons why human genetics does not work

- There are not enough people on the planet
- We have been looking in the wrong place for the genetic effect

Role of Genotype in the Cycle of Violence in Maltreated Children

Avshalom Caspi,[1,2] Joseph McClay,[1] Terrie E. Moffitt,[1,2]*
Jonathan Mill,[1] Judy Martin,[3] Ian W. Craig,[1] Alan Taylor,[1]
Richie Poulton[3]

Science 297:851, 2002

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2]*
Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2]
Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3]
Antony Braithwaite,[4] Richie Poulton[3]

Science 301:386, 2003

Gene X Environment interaction

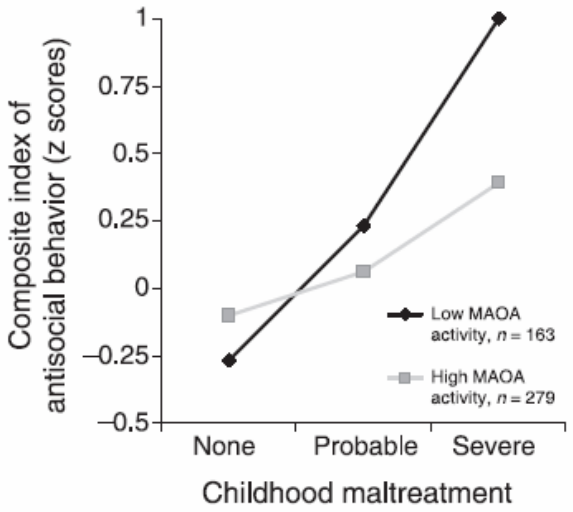


Fig. 1. Means on the composite index of antisocial behavior as a function of *MAOA* activity and a childhood history of maltreatment (*27*). *MAOA* activity is the gene expression level associated with allelic variants of the functional promoter polymorphism, grouped into low and high activity; childhood maltreatment is grouped into 3 categories of increasing severity. The antisocial behavior composite is standardized (z score) to a M = 0 and SD = 1; group differences are interpretable in SD unit differences (d).

G X E interactions

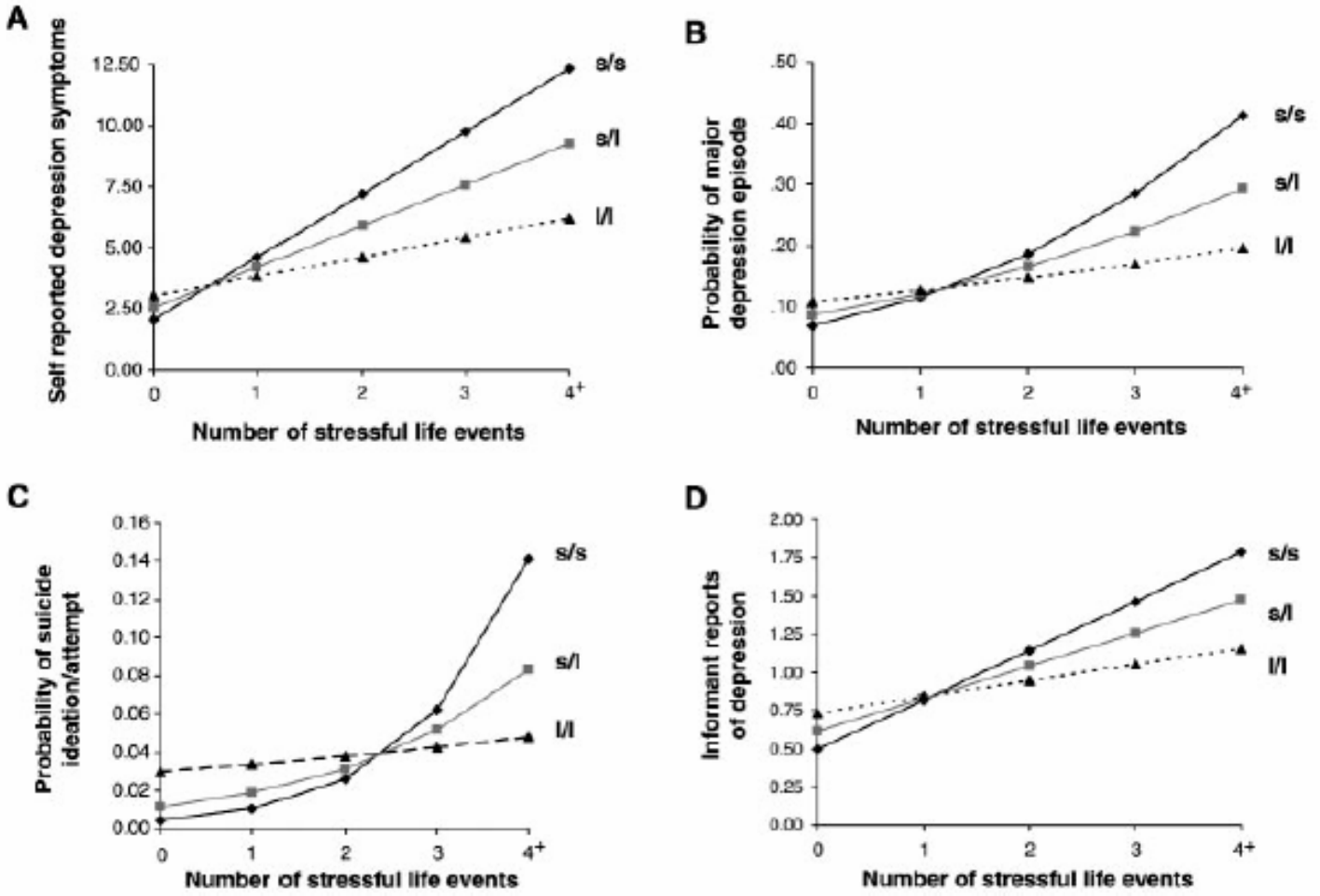


Fig. 1. Results of multiple regression analyses estimating the association between number of stressful life events (between ages 21 and 26 years) and depression outcomes at age 26 as a function of 5-HTT genotype. Among the 146 s/s homozygotes, 43 (29%), 37 (25%), 28 (19%), 15 (10%), and 23 (16%) study members experienced zero, one, two, three, and four or more stressful events, respectively. Among the 435 s/l heterozygotes, 141 (32%), 101 (23%), 76 (17%), 49 (11%), and 68 (16%) experienced zero, one, two, three, and four or more stressful events. Among the 264 l/l homozygotes, 79 (29%), 73 (28%), 57 (21%), 26 (10%), and 29 (11%) experienced zero, one, two, three, and four or more stressful events. (**A**) Self-reports of depression symptoms. The main effect of 5-HTTLPR (i.e., an effect not conditional on other variables) was marginally significant ($b = -0.96$, SE = 0.52, $t = 1.86$, $P = 0.06$), the main effect of stressful life events was significant ($b = 1.75$, SE = 0.23, $t = 7.45$, $P < 0.001$), and the interaction between 5-HTTLPR and life events was in the predicted direction ($b = -0.89$, SE = 0.37, $t = 2.39$, $P = 0.02$). The interaction showed that the effect of life events on self-reports of depression symptoms was stronger among individuals carrying an s allele ($b = 2.52$, SE = 0.66, $t = 3.82$, $P < 0.001$ among s/s homozygotes, and $b = 1.71$, SE = 0.34, $t = 5.02$, $P < 0.001$ among s/l heterozygotes) than among l/l homozygotes ($b = 0.77$, SE = 0.43, $t = 1.79$, $P = 0.08$). (**B**) Probability of major depressive episode. The main effect of 5-HTTLPR was not significant ($b = -0.15$, SE = 0.14, $z = 1.07$, $P = 0.29$), the main effect of life events was significant ($b = 0.37$, SE = 0.06, $z = 5.99$, $P < 0.001$), and the G × E was in the predicted direction ($b = -0.19$, SE = 0.10, $z = 1.91$, $P = 0.056$). Life events predicted a diagnosis of major depression among s carriers ($b = 0.52$, SE = 0.16, $z = 3.28$, $P = 0.001$ among s/s homozygotes, and $b = 0.39$, SE = 0.09, $z = 4.24$, $P < 0.001$ among s/l heterozygotes) but not among l/l homozygotes ($b = 0.16$, SE = 0.13, $z = 1.18$, $P = 0.24$). (**C**) Probability of suicide ideation or attempt. The main effect of 5-HTTLPR was not significant ($b = -0.01$, SE = 0.28, $z = 0.01$, $P = 0.99$), the main effect of life events was significant ($b = 0.51$, SE = 0.13, $z = 3.96$, $P < 0.001$), and the G × E interaction was in the predicted direction ($b = -0.39$, SE = 0.20, $t = 1.95$, $P = 0.051$). Life events predicted suicide ideation or attempt among s carriers ($b = 0.48$, SE = 0.29, $z = 1.67$, $P = 0.09$ among s/s homozygotes, and $b = 0.91$, SE = 0.25, $z = 3.58$, $P < 0.001$ among s/l heterozygotes) but not among l/l homozygotes ($b = 0.13$, SE = 0.26, $z = 0.49$, $P = 0.62$). (**D**) Informant reports of depression. The main effect of 5-HTTLPR was not significant (b = −0.06, SE = 0.06, t = 0.98, $P = 0.33$), the main effect of life events was significant ($b = 0.23$, SE = 0.03, $t = 8.47$, $P < 0.001$), and the G × E was in the predicted direction ($b = -0.11$, SE = 0.04, $t = 2.54$, $P < 0.01$). The effect of life events on depression was stronger among s carriers ($b = 0.39$, SE = 0.07, $t = 5.23$, $P < 0.001$ among s/s homozygotes, and $b = 0.17$, SE = 0.04, $t = 4.51$, $P < 0.001$ among s/l heterozygotes) than among l/l homozygotes ($b = 0.14$, SE = 0.05, $t = 2.69$, $P < 0.01$).

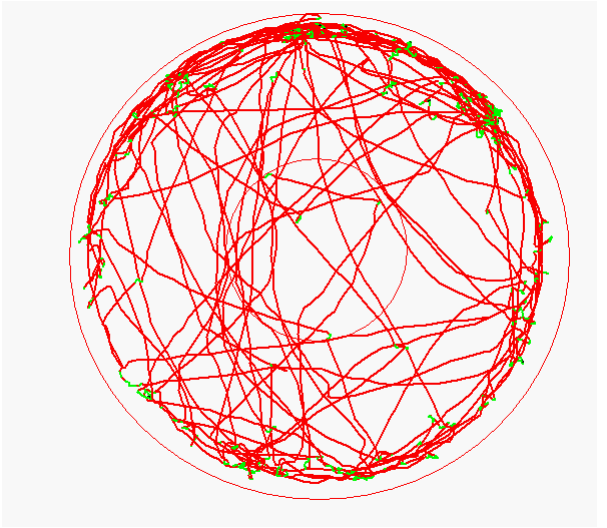
Reasons why human genetics does not work

- There are not enough people on the planet
- Genetic effect is hidden in epistasis
- Genetic effect is hidden in a (small) gene by environment interaction

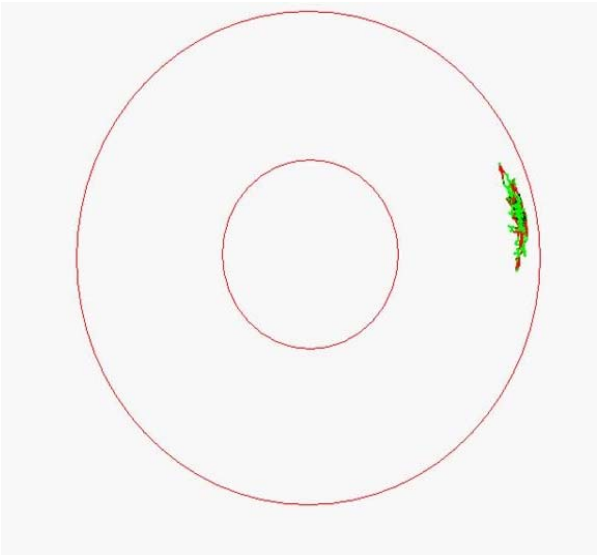
Mouse model of anxiety

Mouse model of anxiety

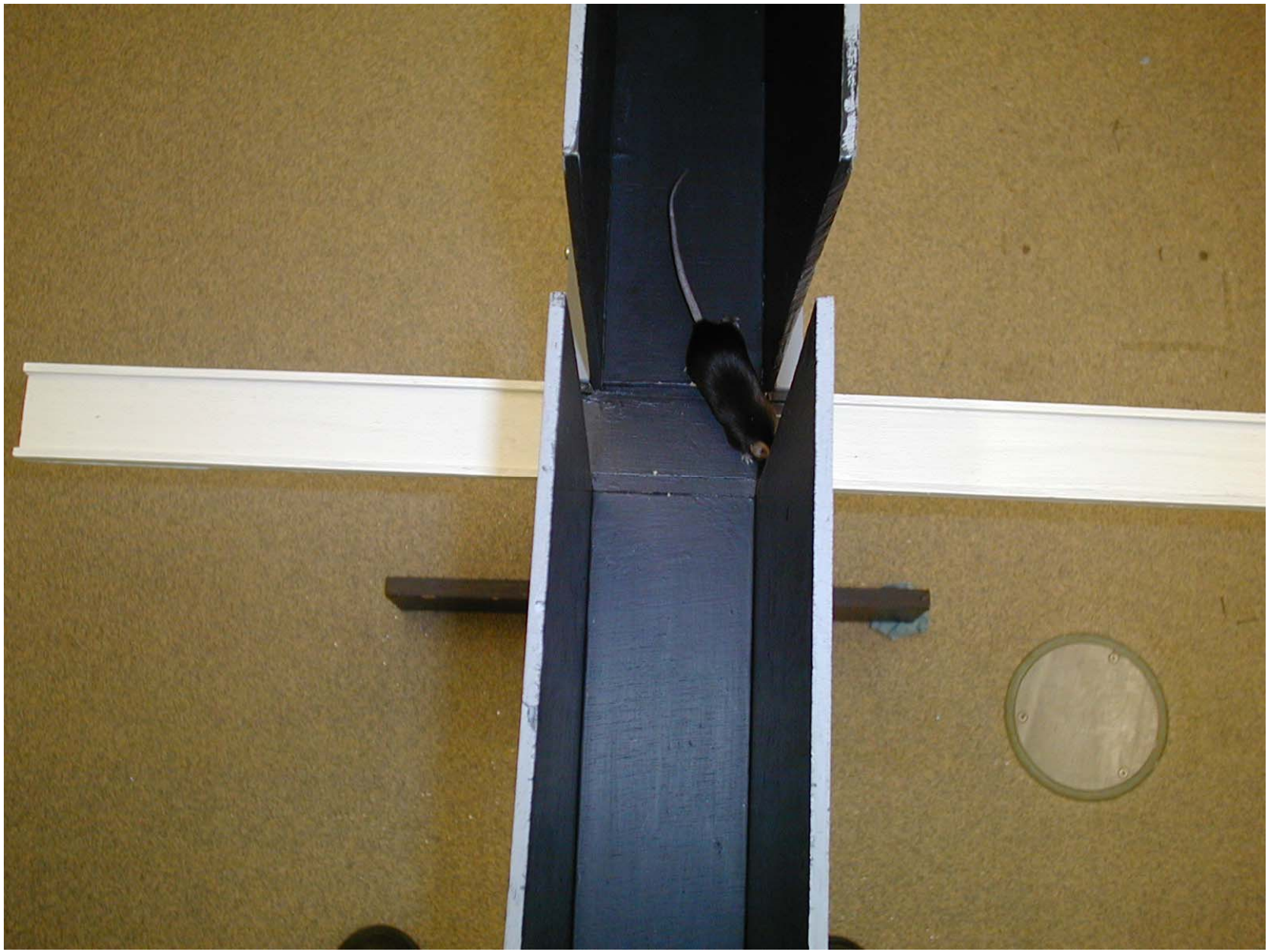
Non anxious mouse

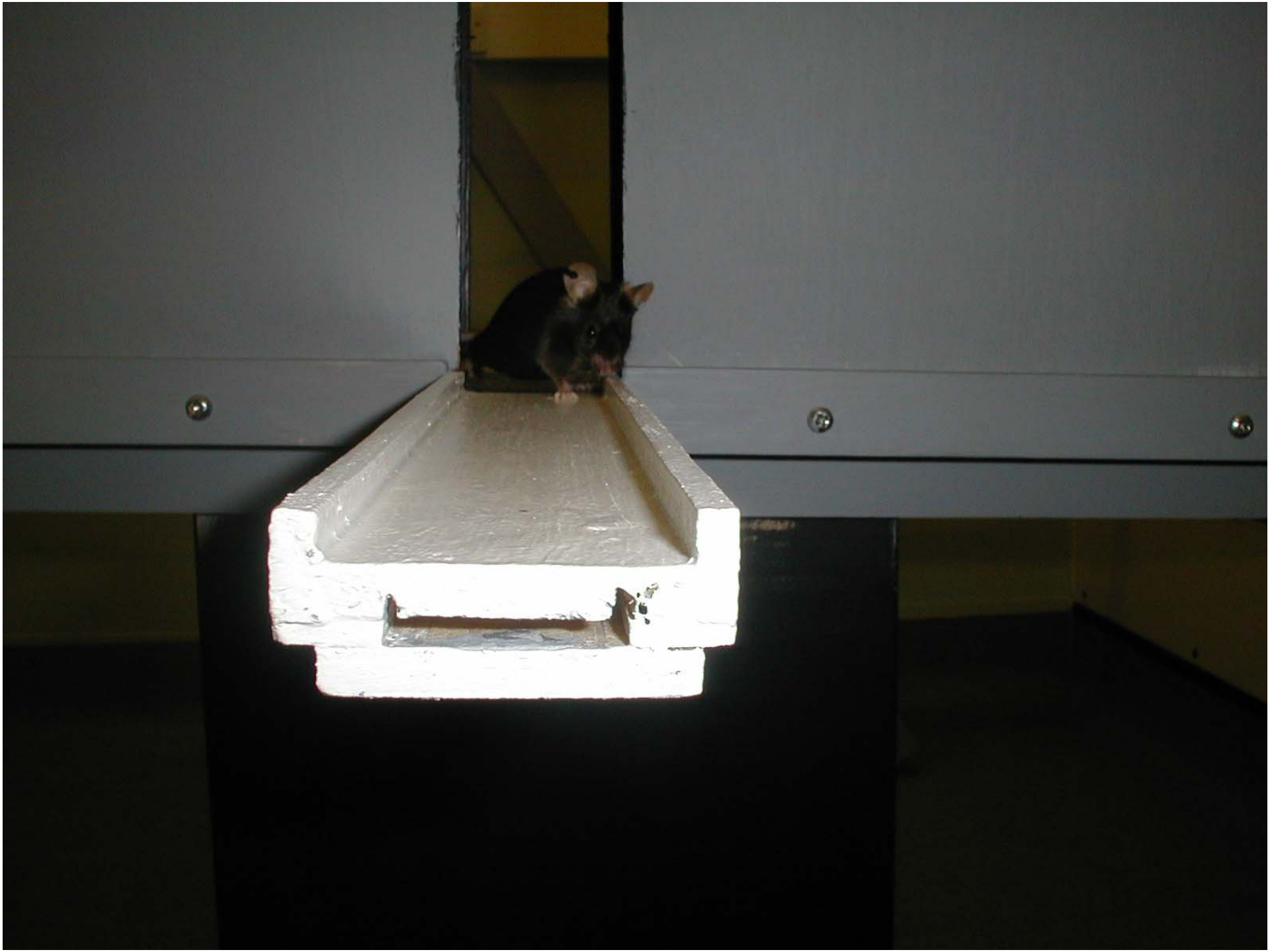


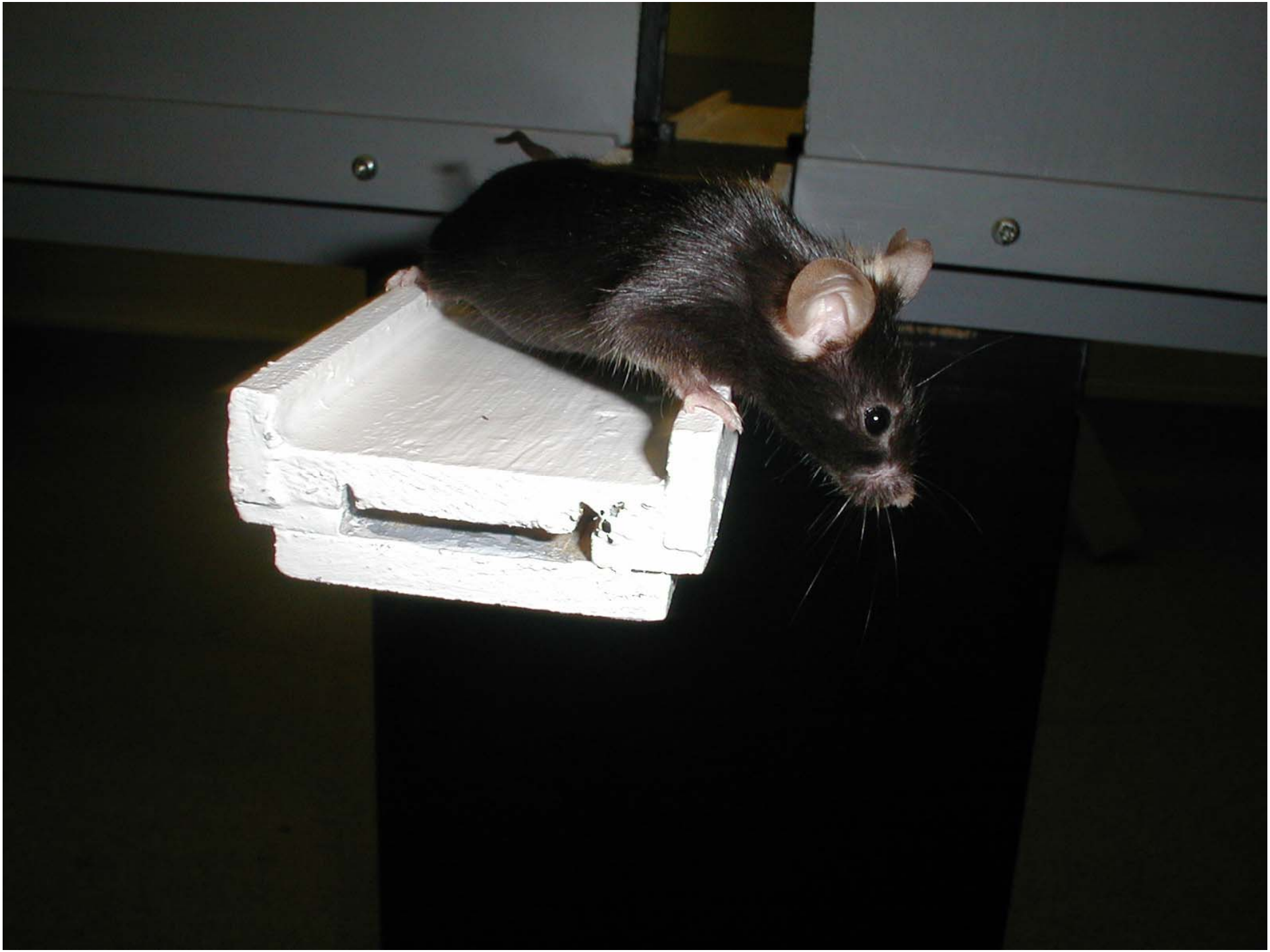
Anxious mouse

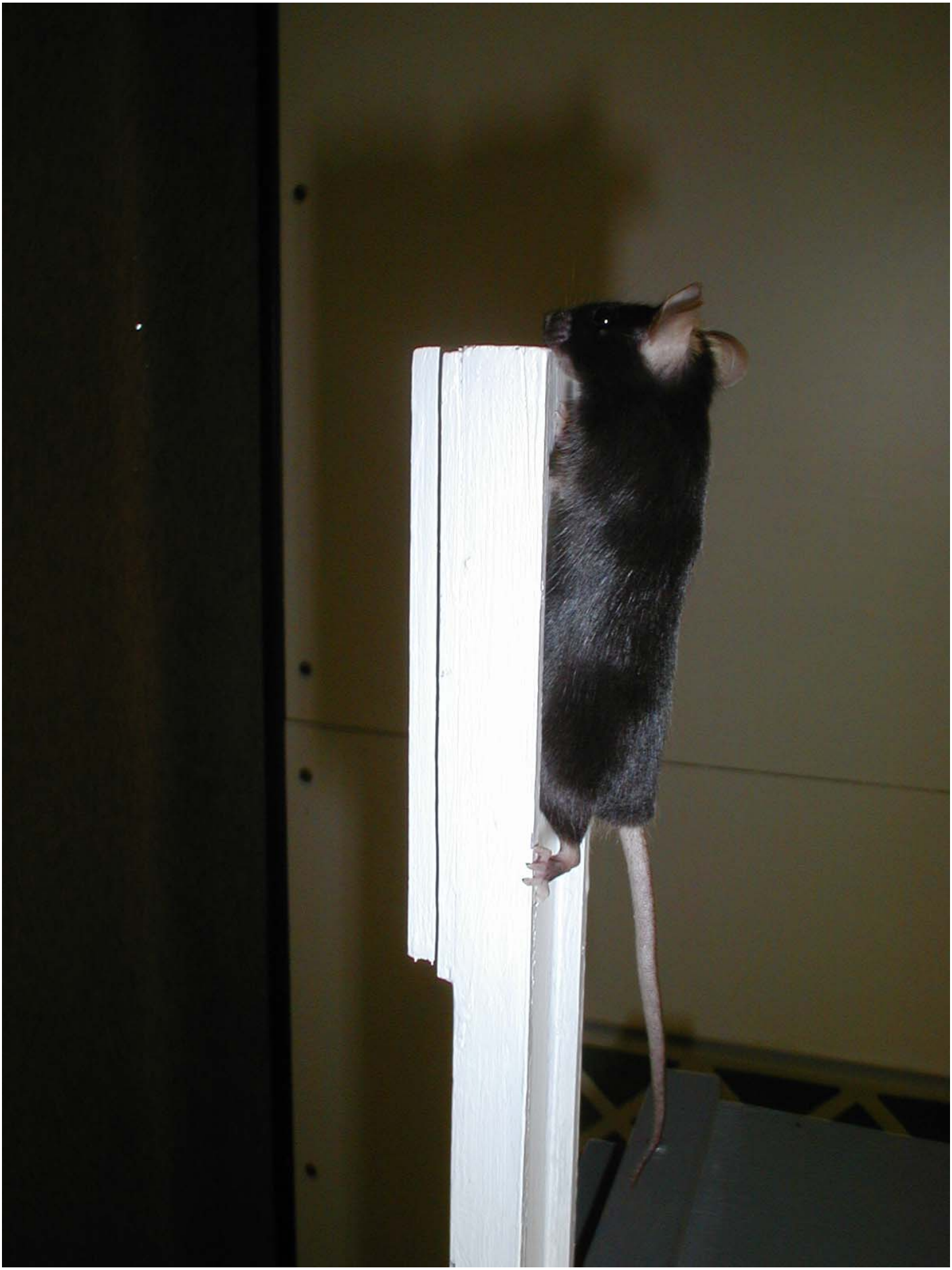


Elevated Plus Maze

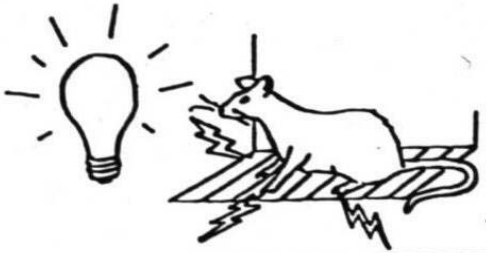






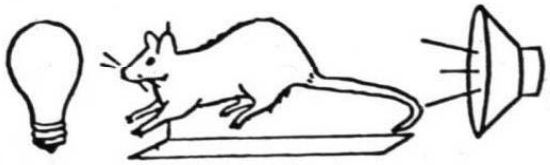


TRAINING: LIGHT and SHOCK PAIRED



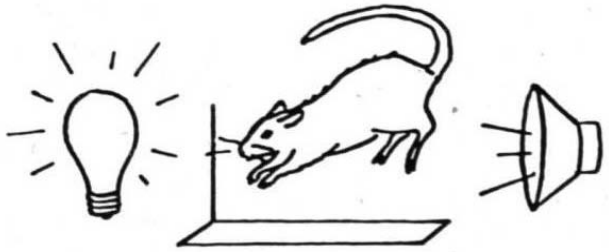
TESTING:

NOISE-ALONE TRIALS



NORMAL STARTLE (in dark)

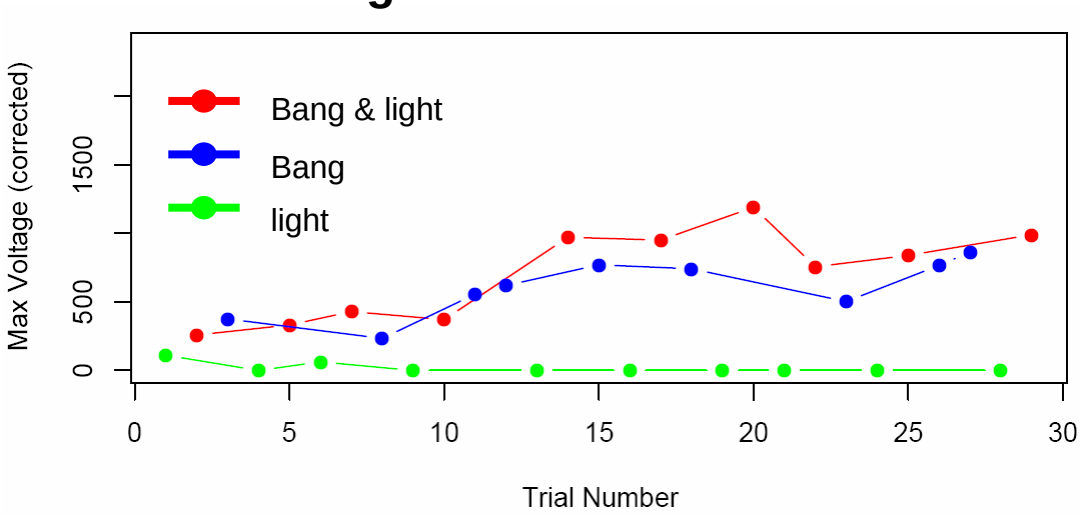
LIGHT-NOISE TRIALS



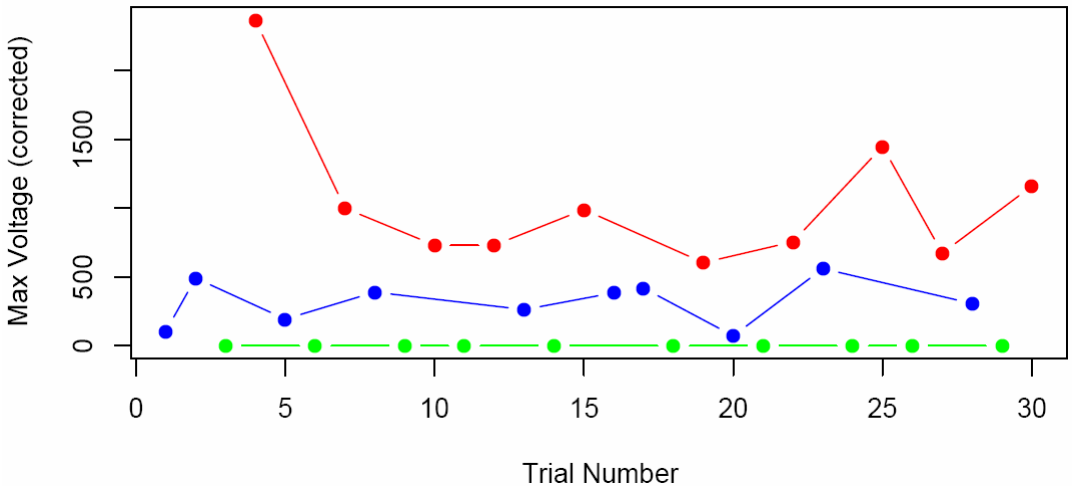
POTENTIATED STARTLE (in light)

Startle and its potentiation

Pretraining



Test



Reasons why human genetics does not work

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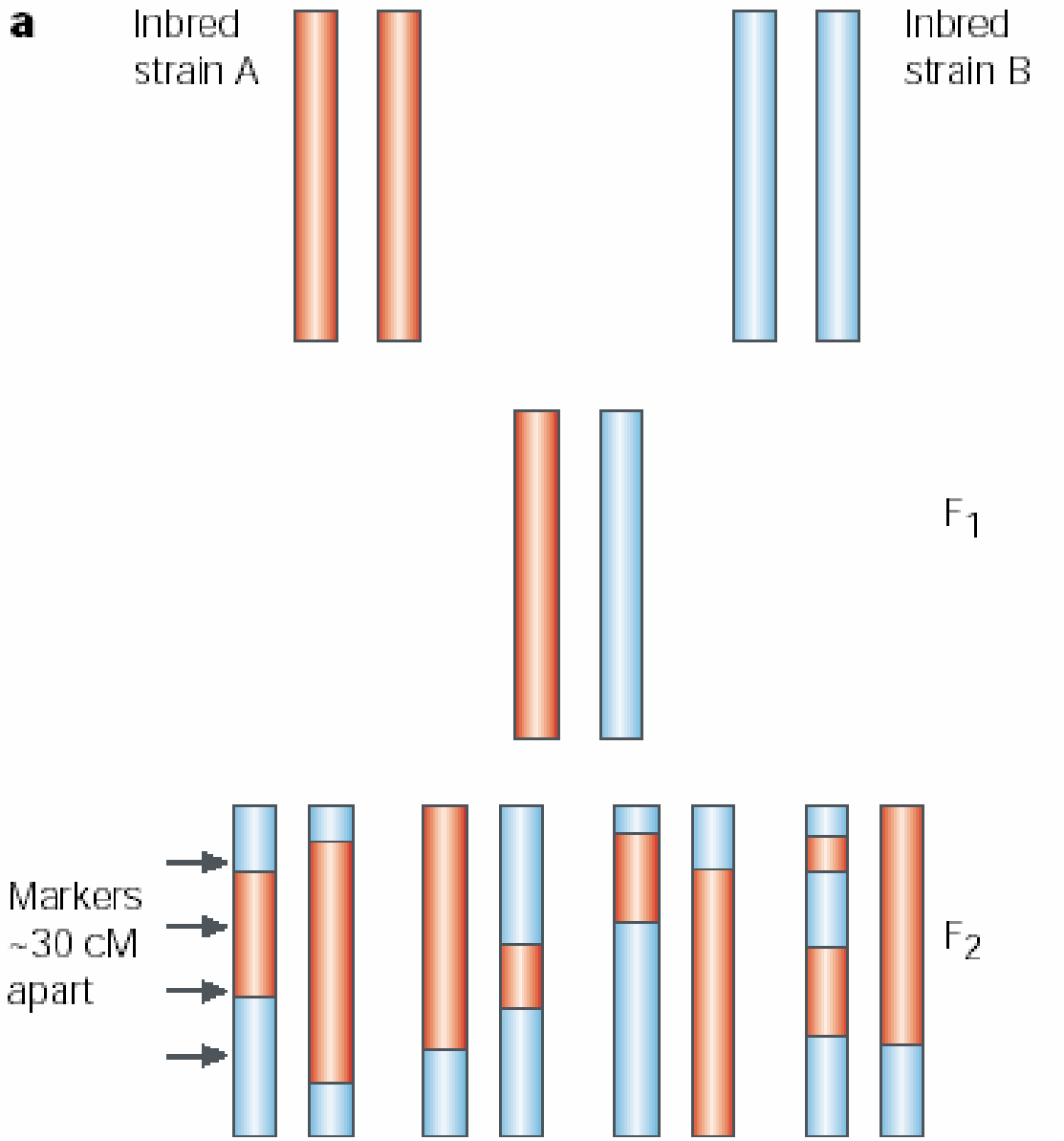
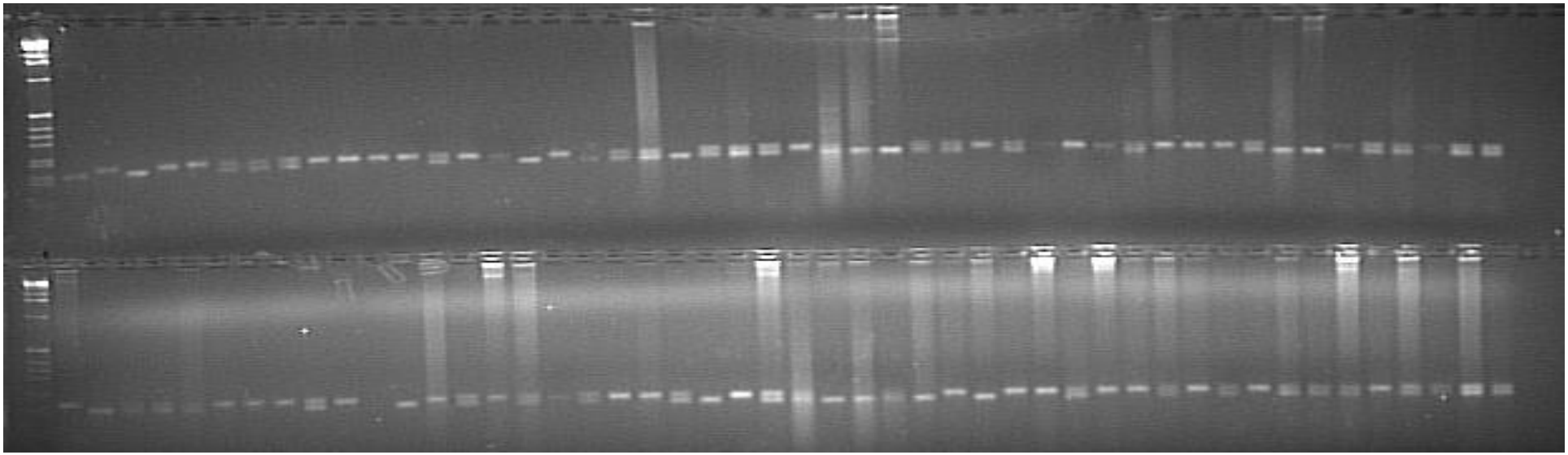
Genetic architecture of complex traits

- Effect sizes and number of loci

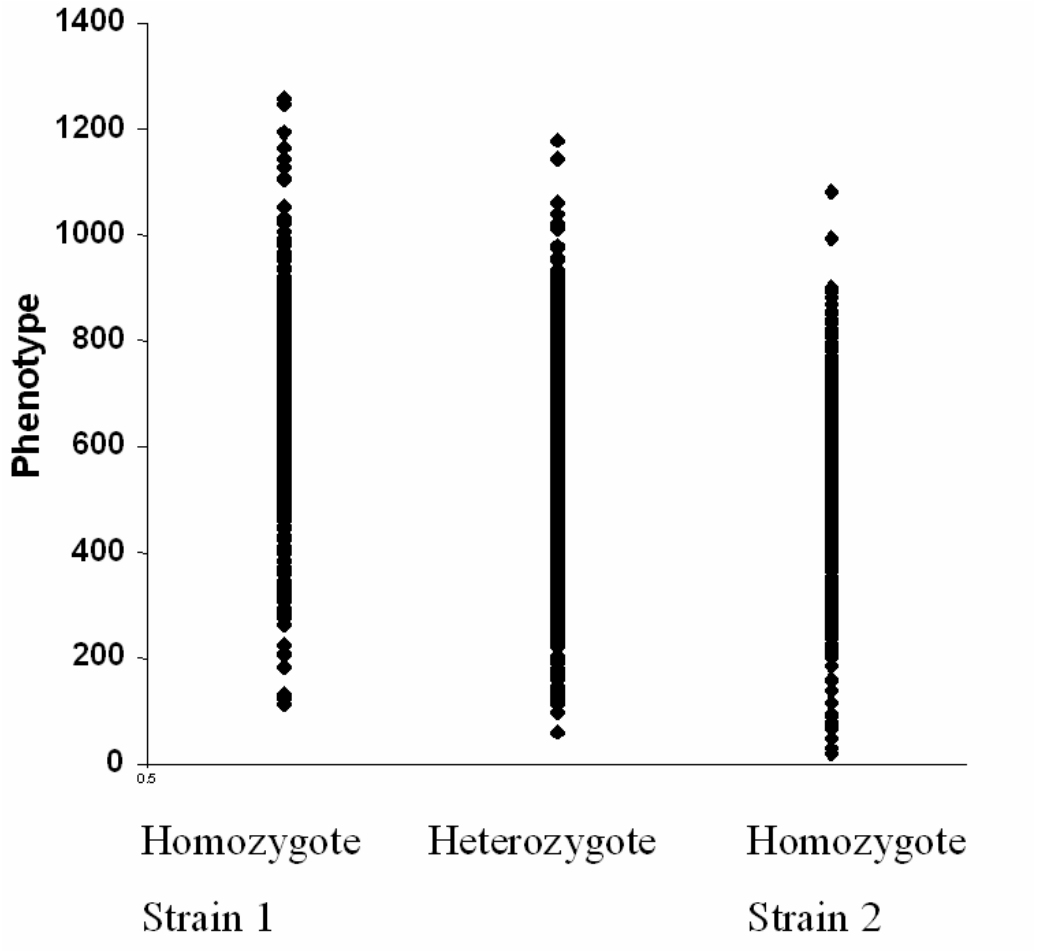
Inbred Strain Cross

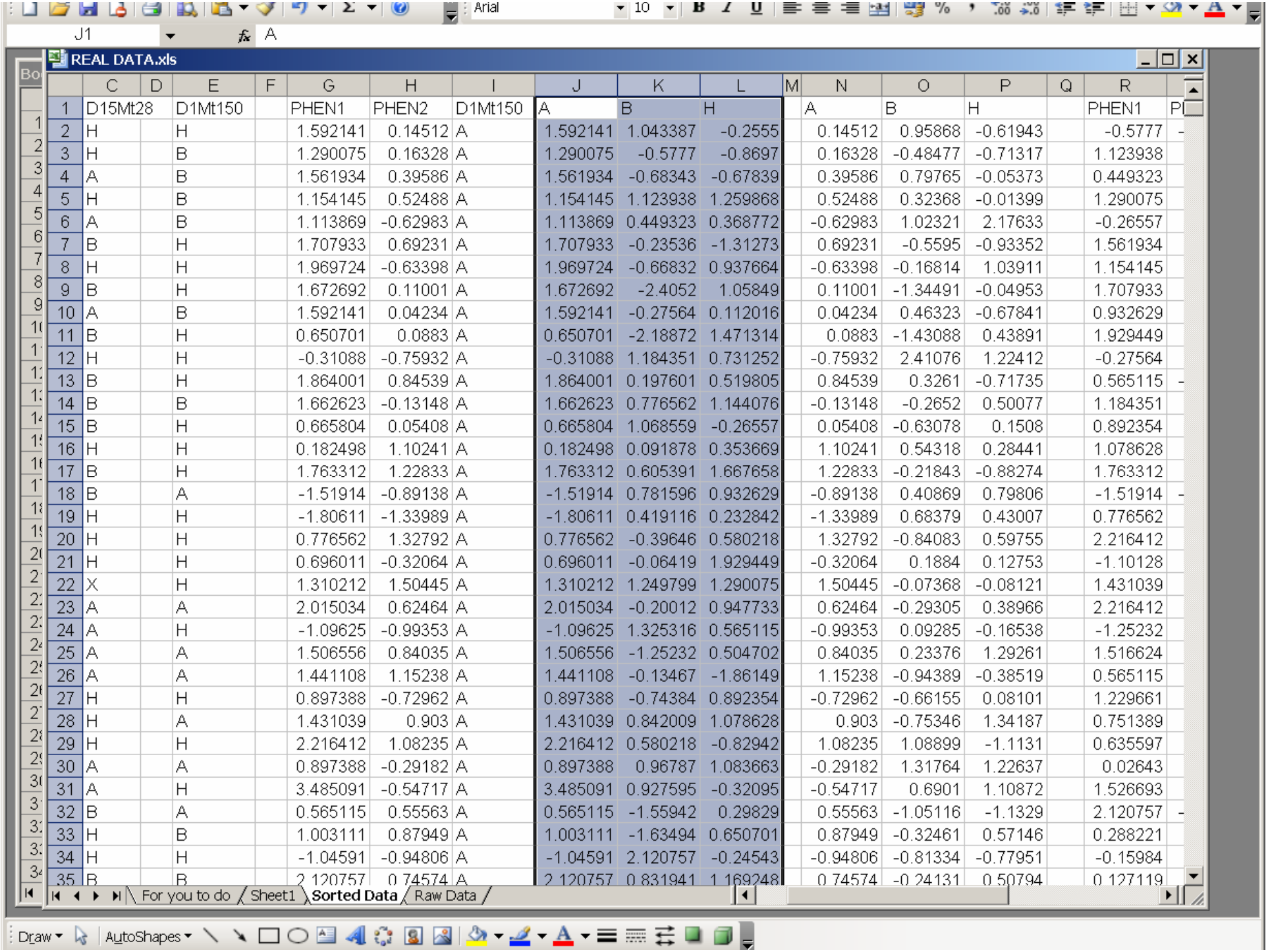


Quantitative Trait Locus Detection



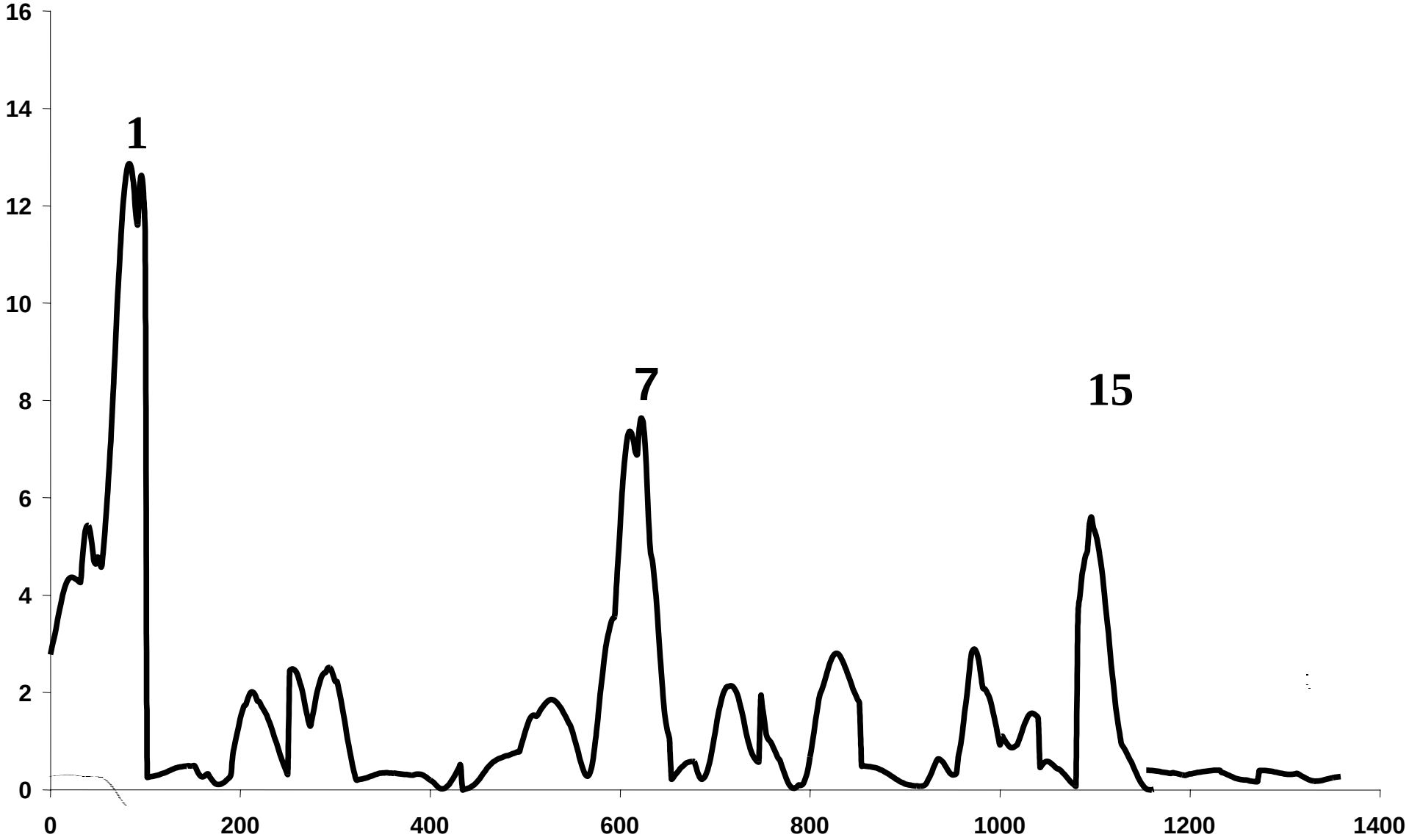
QTL Mapping: single marker analysis

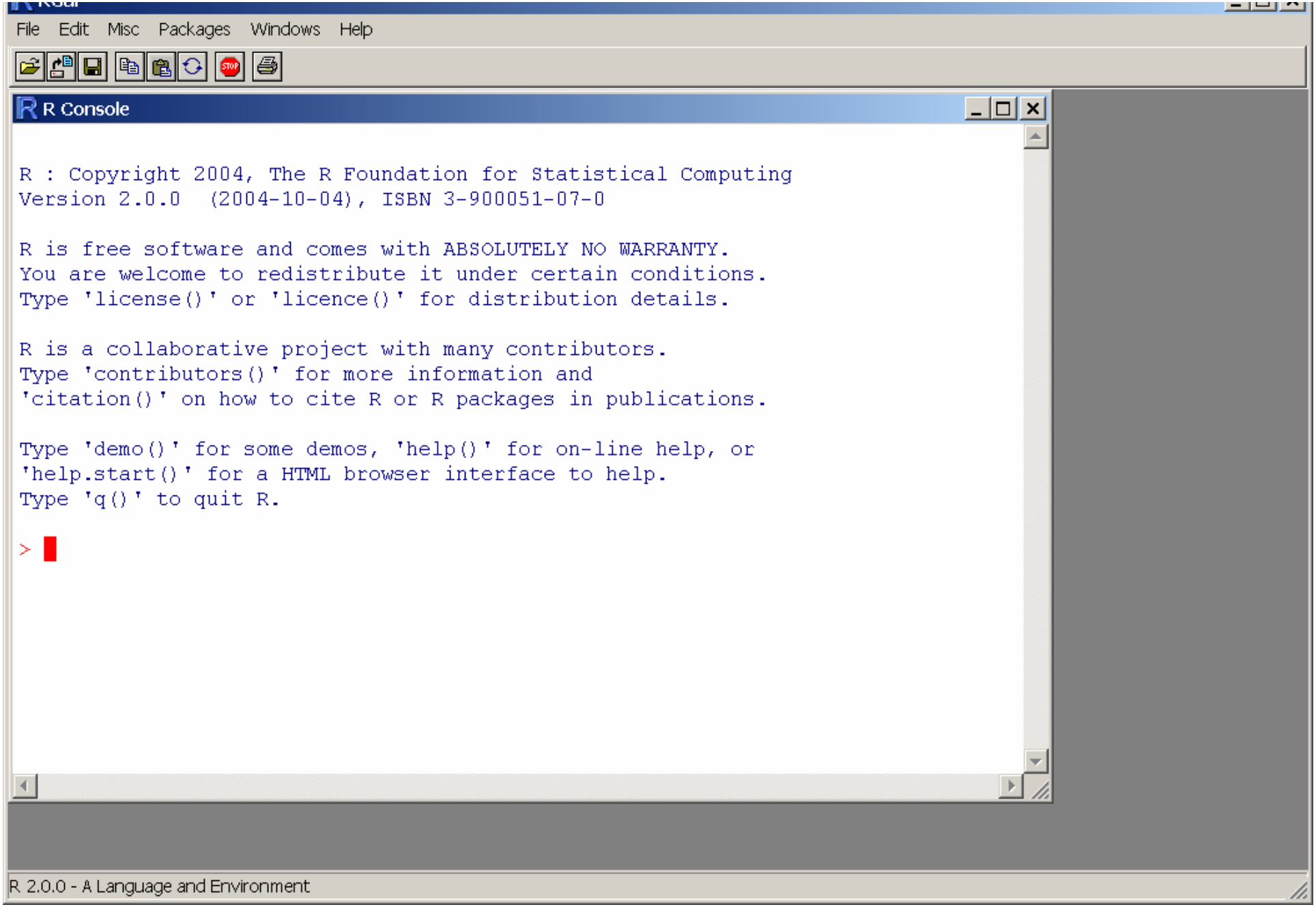




	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
1	D15Mt28		D1Mt150		PHEN1	PHEN2	D1Mt150	A	B	H		A	B	H		PHEN1
2	H		H		1.592141	0.14512	A	1.592141	1.043387	-0.2555		0.14512	0.95868	-0.61943		-0.5777
3	H		B		1.290075	0.16328	A	1.290075	-0.5777	-0.8697		0.16328	-0.48477	-0.71317		1.123938
4	A		B		1.561934	0.39586	A	1.561934	-0.68343	-0.67839		0.39586	0.79765	-0.05373		0.449323
5	H		B		1.154145	0.52488	A	1.154145	1.123938	1.259868		0.52488	0.32368	-0.01399		1.290075
6	A		B		1.113869	-0.62983	A	1.113869	0.449323	0.368772		-0.62983	1.02321	2.17633		-0.26557
7	B		H		1.707933	0.69231	A	1.707933	-0.23536	-1.31273		0.69231	-0.5595	-0.93352		1.561934
8	H		H		1.969724	-0.63398	A	1.969724	-0.66832	0.937664		-0.63398	-0.16814	1.03911		1.154145
9	B		H		1.672692	0.11001	A	1.672692	-2.4052	1.05849		0.11001	-1.34491	-0.04953		1.707933
10	A		B		1.592141	0.04234	A	1.592141	-0.27564	0.112016		0.04234	0.46323	-0.67841		0.932629
11	B		H		0.650701	0.0883	A	0.650701	-2.18872	1.471314		0.0883	-1.43088	0.43891		1.929449
12	H		H		-0.31088	-0.75932	A	-0.31088	1.184351	0.731252		-0.75932	2.41076	1.22412		-0.27564
13	B		H		1.864001	0.84539	A	1.864001	0.197601	0.519805		0.84539	0.3261	-0.71735		0.565115
14	B		B		1.662623	-0.13148	A	1.662623	0.776562	1.144076		-0.13148	-0.2652	0.50077		1.184351
15	B		H		0.665804	0.05408	A	0.665804	1.068559	-0.26557		0.05408	-0.63078	0.1508		0.892354
16	H		H		0.182498	1.10241	A	0.182498	0.091878	0.353669		1.10241	0.54318	0.28441		1.078628
17	B		H		1.763312	1.22833	A	1.763312	0.605391	1.667658		1.22833	-0.21843	-0.88274		1.763312
18	B		A		-1.51914	-0.89138	A	-1.51914	0.781596	0.932629		-0.89138	0.40869	0.79806		-1.51914
19	H		H		-1.80611	-1.33989	A	-1.80611	0.419116	0.232842		-1.33989	0.68379	0.43007		0.776562
20	H		H		0.776562	1.32792	A	0.776562	-0.39646	0.580218		1.32792	-0.84083	0.59755		2.216412
21	H		H		0.696011	-0.32064	A	0.696011	-0.06419	1.929449		-0.32064	0.1884	0.12753		-1.10128
22	X		H		1.310212	1.50445	A	1.310212	1.249799	1.290075		1.50445	-0.07368	-0.08121		1.431039
23	A		A		2.015034	0.62464	A	2.015034	-0.20012	0.947733		0.62464	-0.29305	0.38966		2.216412
24	A		H		-1.09625	-0.99353	A	-1.09625	1.325316	0.565115		-0.99353	0.09285	-0.16538		-1.25232
25	A		A		1.506556	0.84035	A	1.506556	-1.25232	0.504702		0.84035	0.23376	1.29261		1.516624
26	A		A		1.441108	1.15238	A	1.441108	-0.13467	-1.86149		1.15238	-0.94389	-0.38519		0.565115
27	H		H		0.897388	-0.72962	A	0.897388	-0.74384	0.892354		-0.72962	-0.66155	0.08101		1.229661
28	H		A		1.431039	0.903	A	1.431039	0.842009	1.078628		0.903	-0.75346	1.34187		0.751389
29	H		H		2.216412	1.08235	A	2.216412	0.580218	-0.82942		1.08235	1.08899	-1.1131		0.635597
30	A		A		0.897388	-0.29182	A	0.897388	0.96787	1.083663		-0.29182	1.31764	1.22637		0.02643
31	A		H		3.485091	-0.54717	A	3.485091	0.927595	-0.32095		-0.54717	0.6901	1.10872		1.526693
32	B		A		0.565115	0.55563	A	0.565115	-1.55942	0.29829		0.55563	-1.05116	-1.1329		2.120757
33	H		B		1.003111	0.87949	A	1.003111	-1.63494	0.650701		0.87949	-0.32461	0.57146		0.288221
34	H		H		-1.04591	-0.94806	A	-1.04591	2.120757	-0.24543		-0.94806	-0.81334	-0.77951		-0.15984
35	B		B		2.120757	0.74574	A	2.120757	0.831941	1.169248		0.74574	-0.24131	0.50794		0.127119

Genome-wide mapping

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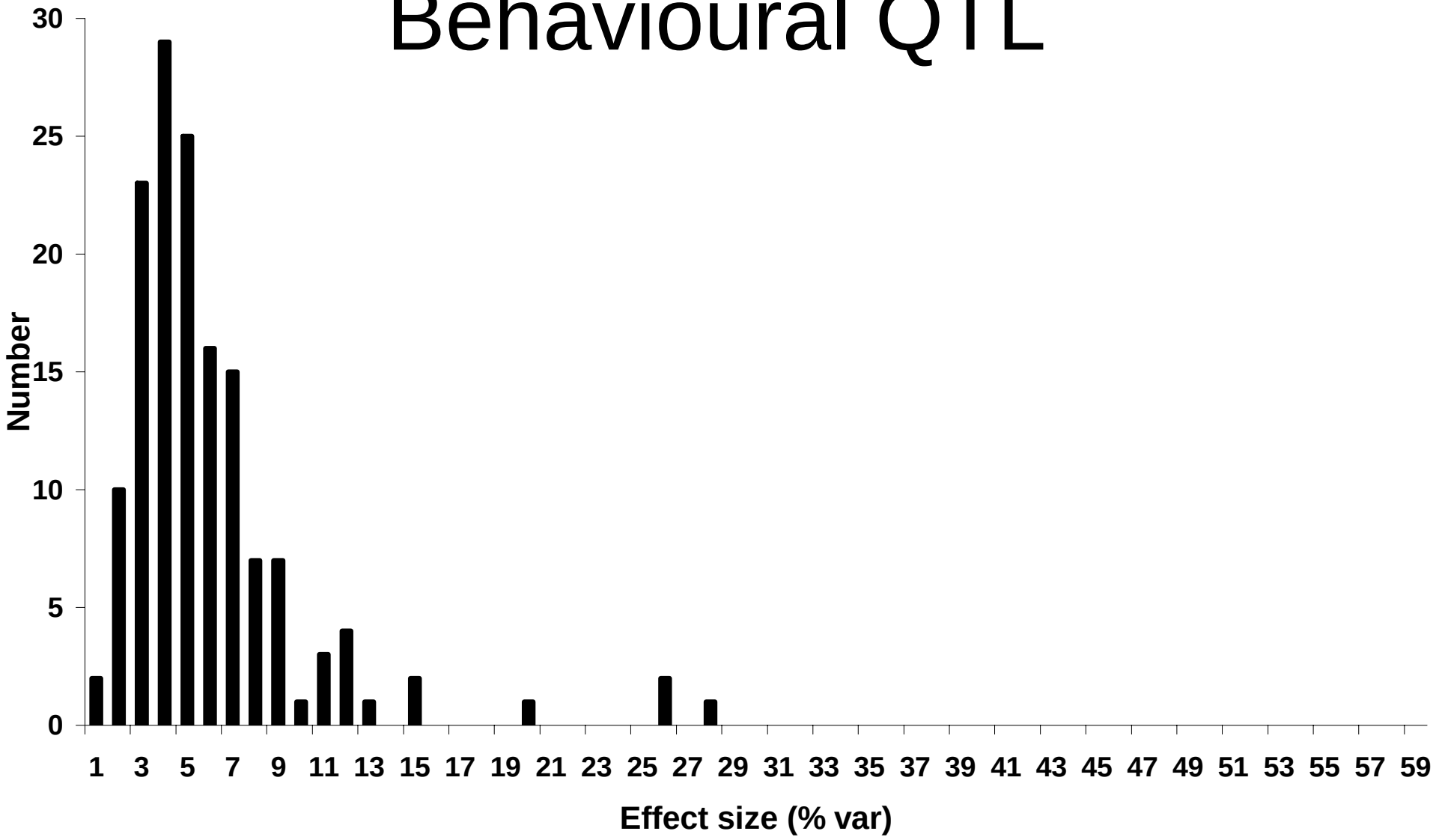
Behavioural QTL



Physiological QTL

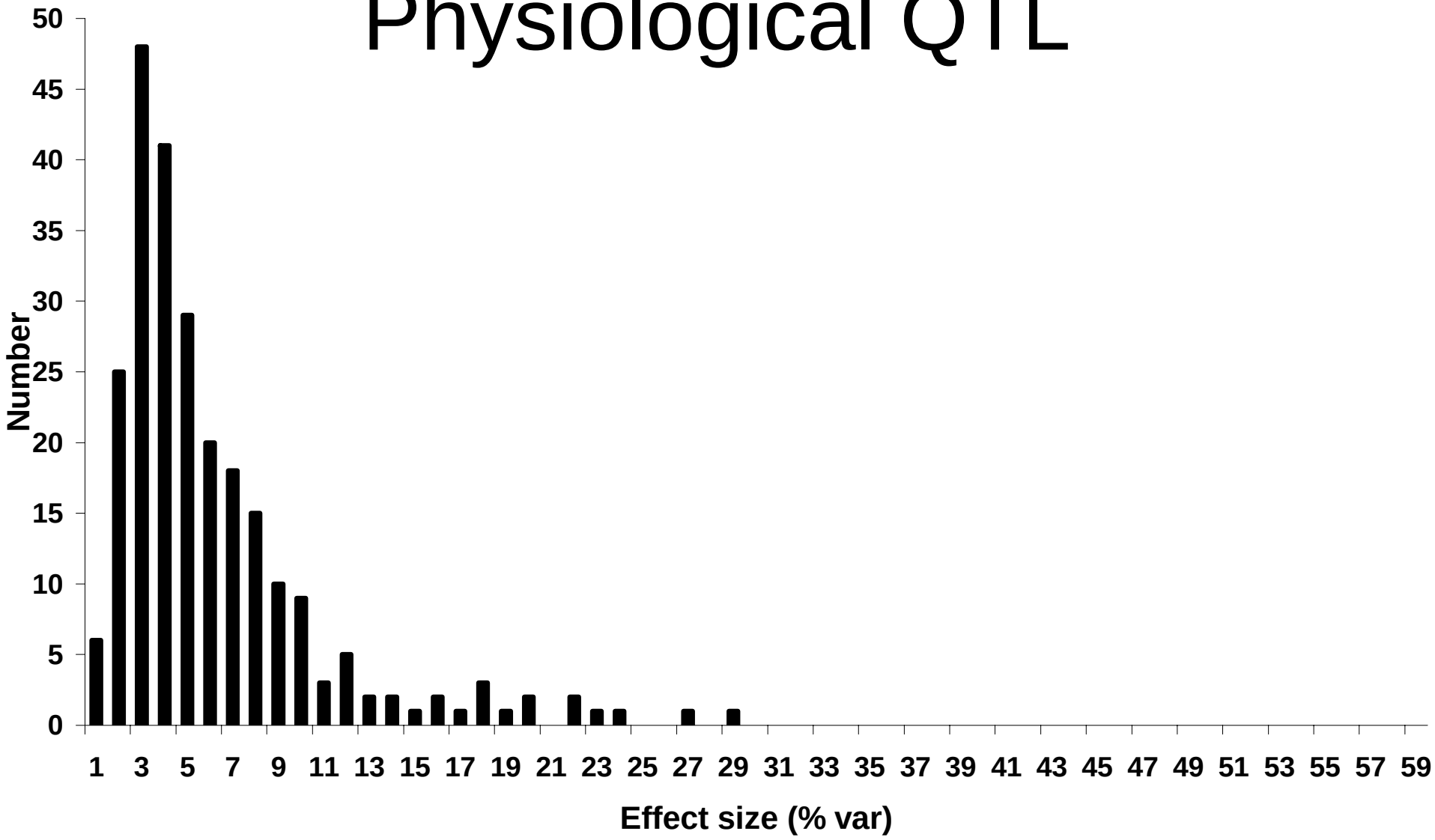


Table 4. QTL estimator. D is the estimate of additive genetic effects, calculated as half the difference between parental phenotypes. The mean QTL effect and minimum QTL effect are the additive effects (not the percentage variation explained by the locus), derived from univariate analyses of each phenotype. The estimated number of QTL is from equation 6, and the 95% confidence intervals (95% CI) are from equation 9 of Otto and Jones (2000). An exponential distribution of effect sizes was assumed

Phenotype	*D*	*Mean QTL effect*	*Minimum QTL effect*	*Observed number QTL*	*Estimated number QTL*	*95% CI*
OF	1.8	0.3	0.1	4	6.4	2–13
Defecation	1.8	0.3	0.1	4	6.4	2–13
Total activity	362.5	62.1	25.8	7	8.6	4–15
Center activity	162.8	38.3	12.1	4	4.7	2–10
Center time	30.8	5.8	2.5	5	7.1	3–10
Latency	44.7	15.9	12.7	2	9.3	2–18
LD	35.0	6.1	2.5	5	8.1	3–16
Dark activity	35.0	6.1	2.5	5	8.1	3–16
Transitions	6.7	1.7	0.7	4	6.2	3–12
Light activity	50.5	15.0	6.9	5	5.0	2–10
Light time	24.1	8.7	6.5	7	9.0	2–14
Latency	96.3	18.3	10.1	5	9.8	1–19
EPM	3.1	1.4	1.1	5	7.6	
Closed entries	3.1	1.4	1.1	5	7.6	1–10
Closed activity	10.6	5.7	4.0	5	4.9	3–11
Open entries	8.2	1.8	0.5	3	4.9	1–11
Open activity	34.1	2.9	0.6	5	8.4	4–25
Open latency	46.7	11.3	2.3	1	4.1	2–9
Open time	62.2	12.6	3.4	3	5.1	1–12
SQ	16.6	4.8	2.6	4	5.6	
Closed entries	16.6	4.8	2.6	4	5.6	2–13
Closed activity	29.2	5.6	1.2	7	5.7	2–10
Open entries	35.4	9.1	4.7	4	6.0	2–14
Open activity	59.9	8.0	2.0	6	7.9	3–18
Latency	47.9	15.0	6.4	2	4.2	2–9
MR	9.2	3.9	2.8	4	6.2	2–14
Entries	9.2	3.9	2.8	4	6.2	2–14
Latency	45.8	9.6	5.7	3	7.7	1–20

Genetic architecture of complex traits in mice

- Genetic effects are small (<5%) and they are lots of them

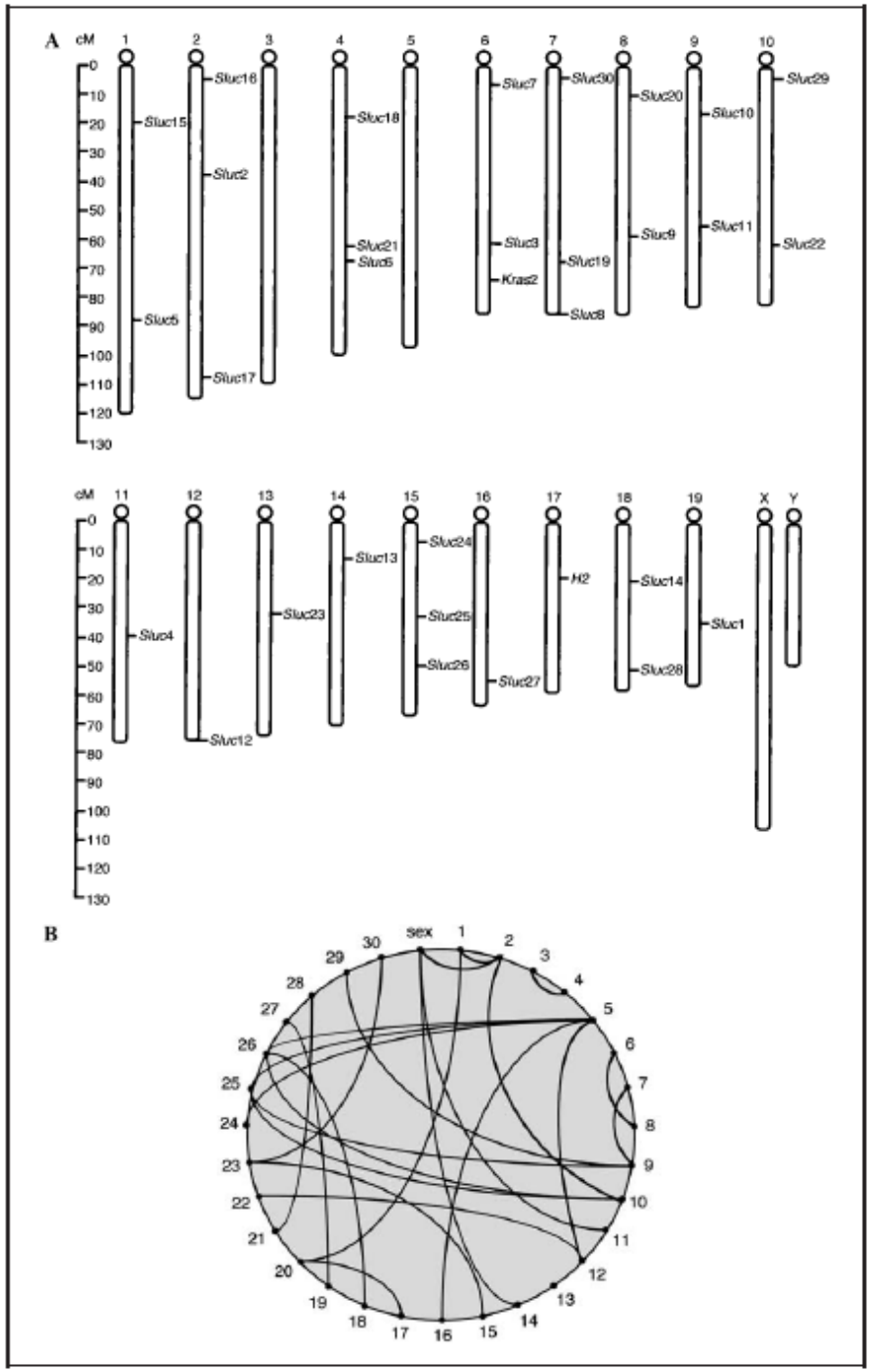
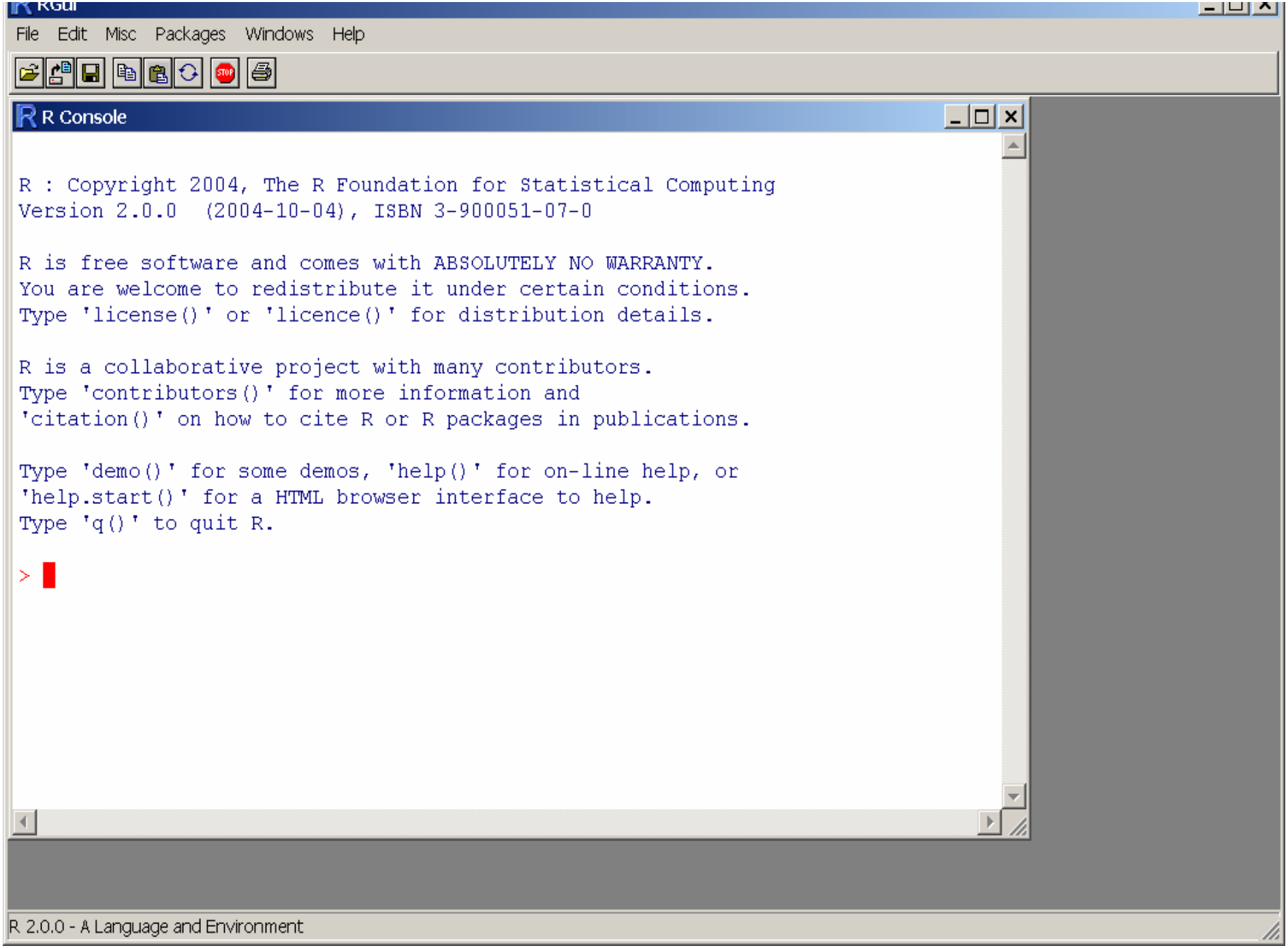


Fig. 1. Lung cancer susceptibility (Sluc) loci in the mouse. **A**) Schematic idiogram of the mouse genome and the location of the 30 Sluc loci detected by using the recombinant congenic strain system. The Kras2 and the H-2 loci are also included. The average minimal candidate Sluc locus region (± standard deviation) is 10.5 (±8) cM, and the average maximal region (± standard deviation) is 19.9 (±9.9) cM, and eight of these Sluc loci are mapped in regions of 12 cM or less. **B**) Schematic representation of all detected interactions between Sluc loci (numbers correspond to Sluc locus numbers from Table 1 and from references *(8–10)*. Sluc6, Sluc8, and Sluc13 *(9)* (main effect only) influence the number of lung tumors, whereas all of the other loci influence the size of the lung tumors. The **linking lines** denote interactions.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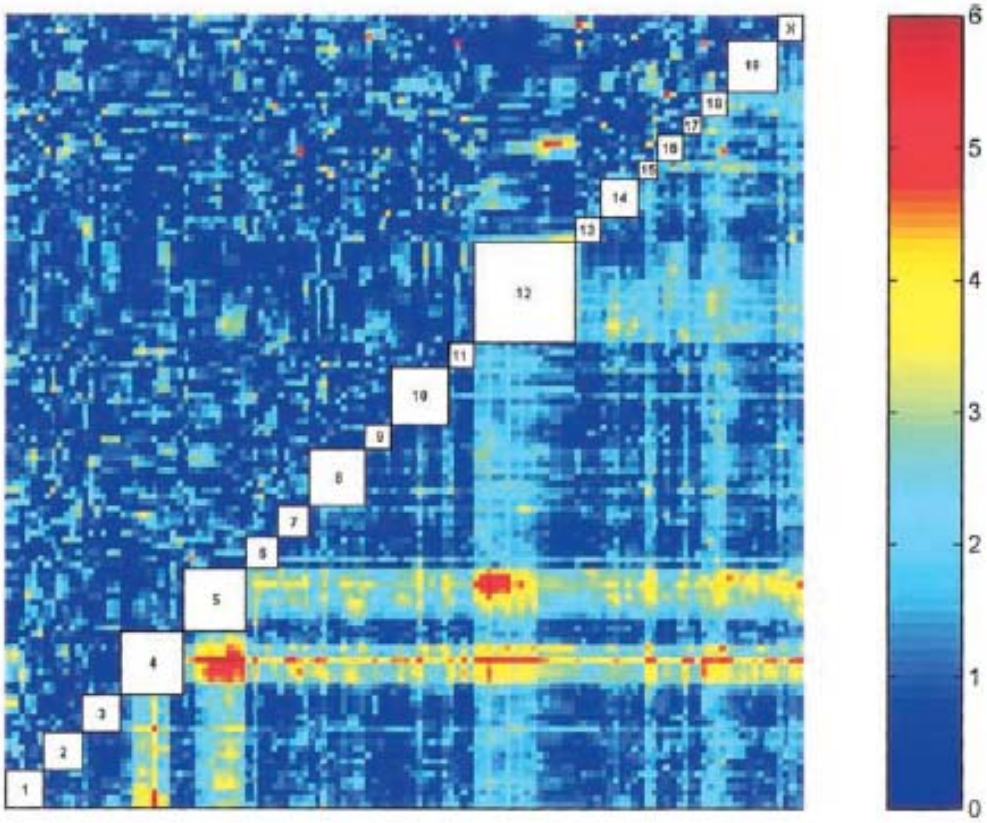
Epistasis in an F2 intercross



Genome-Wide Epistatic Interaction Analysis Reveals Complex Genetic Determinants of Circadian Behavior in Mice

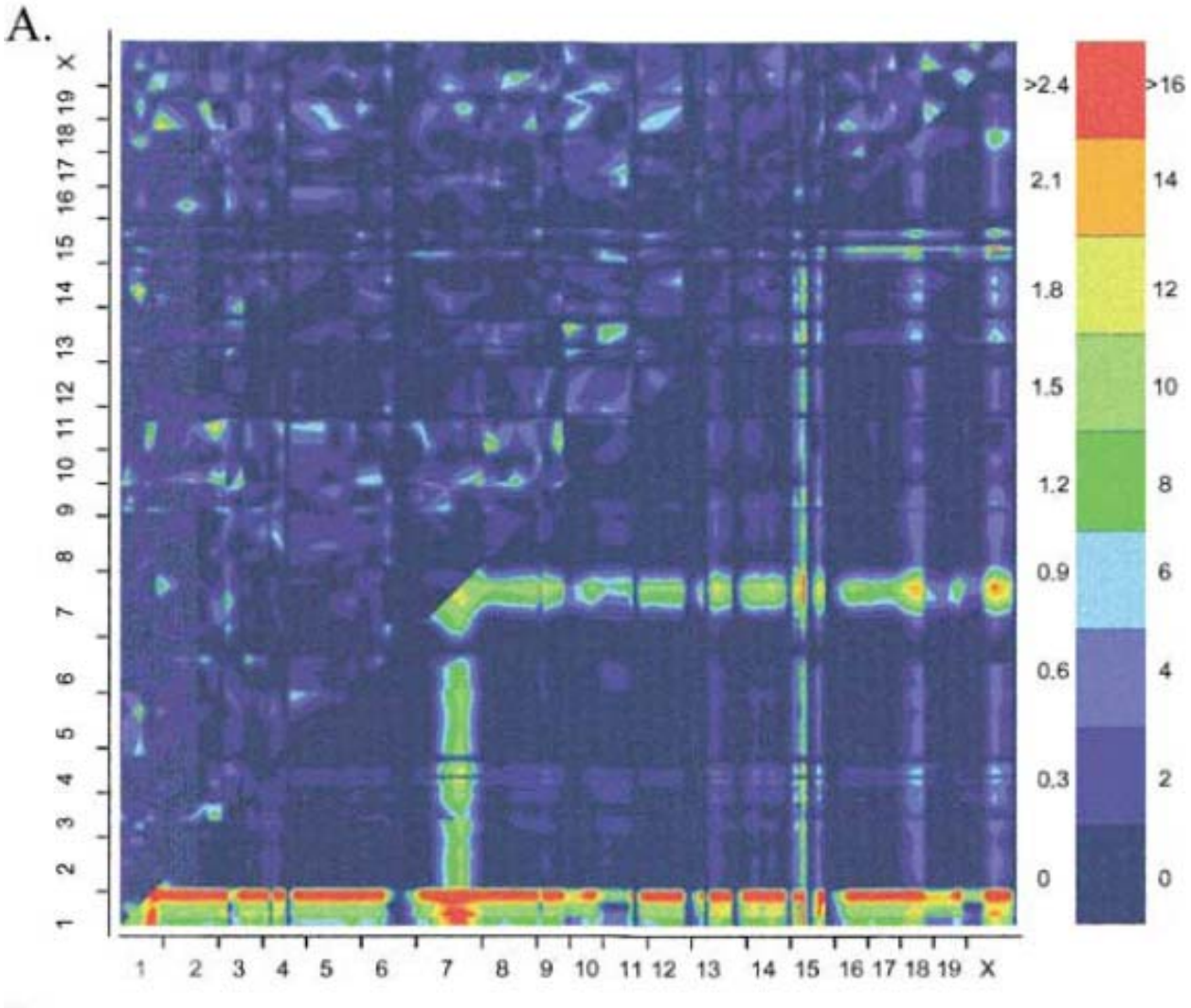
Kazuhiro Shimomura,[1,2] Sharon S. Low-Zeddies,[2] David P. King,[1,2] Thomas D.L. Steeves,[1] Andrew Whiteley,[1] Jani Kushla,[1] Peter D. Zemenides,[2] Andrew Lin,[2] Martha Hotz Vitaterna,[2] Gary A. Churchill,[3] and Joseph S. Takahashi[1,2,4]

Genome Research 11:959–980 ©2001

Table 3. Summary of Significant Marker Pair from Genome-Wide Interaction Analysis

Trait	Marker1	Marker2	F-all	F-int
Period	D4Mit178	D5Mit188	6.57	1.78
	D4Mit178	D12Mit236	5.54	1.36
	D5Mit98	D12Mit236	5.73	3.06
Phase	D7Mit30	D12Mit81	5.77	2.65
	D8Mit13	D12Mit263	5.23	5.89
	D12Mit81	D18Mit17	6.21	2.43
	D12Mit195	D18Mit17	5.47	2.22
Amplitude	D1Mit33	D4Mit27	6.46	6.88
Activity	D16Mit106	DXMit27	5.04	7.23
Dissociation	D12Mit251	D15Mit28	5.90	8.80

Significance of F-all is assessed by permutation analysis. See text for threshold values.
The alpha = 0.01 critical value for F-int is 3.42.



Mammalian Genome Volume 15, 77–82 (2004)

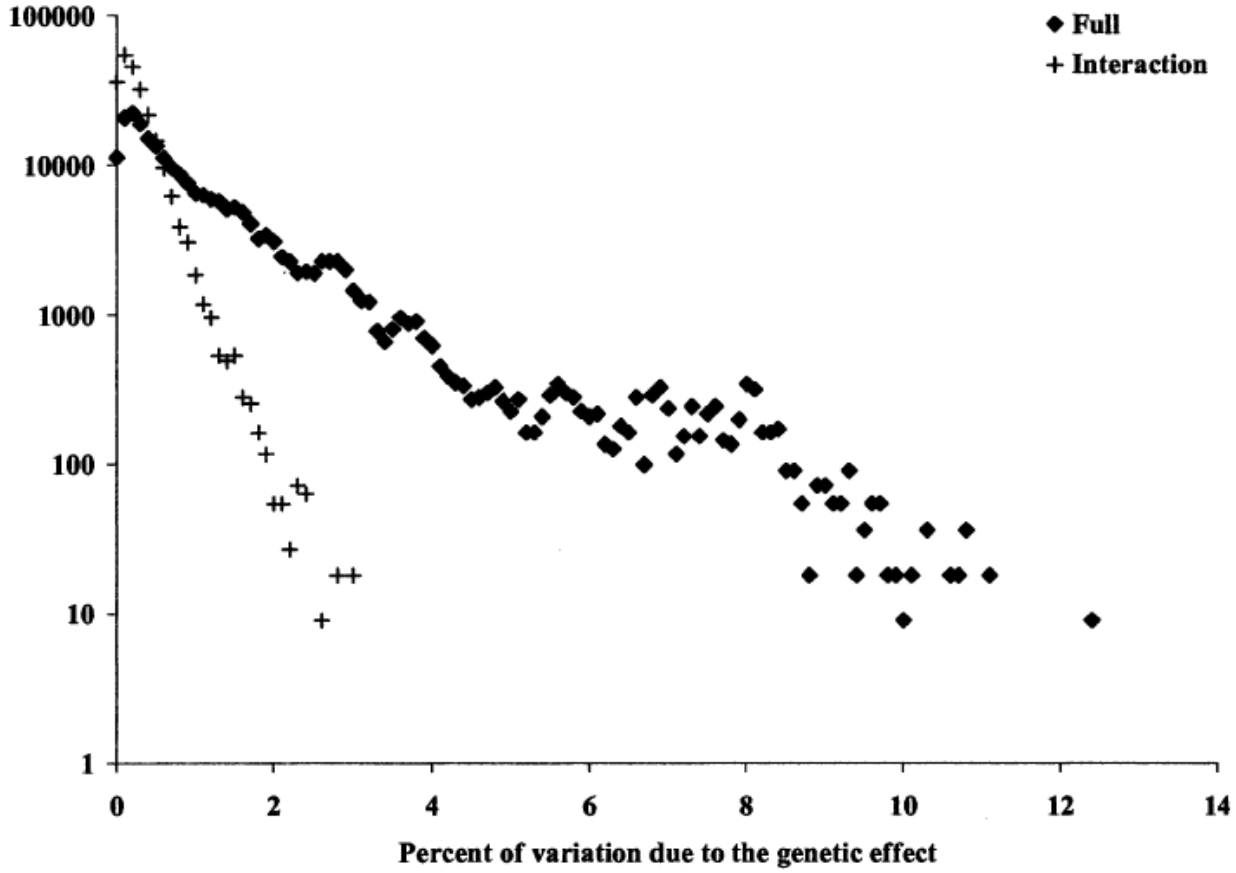
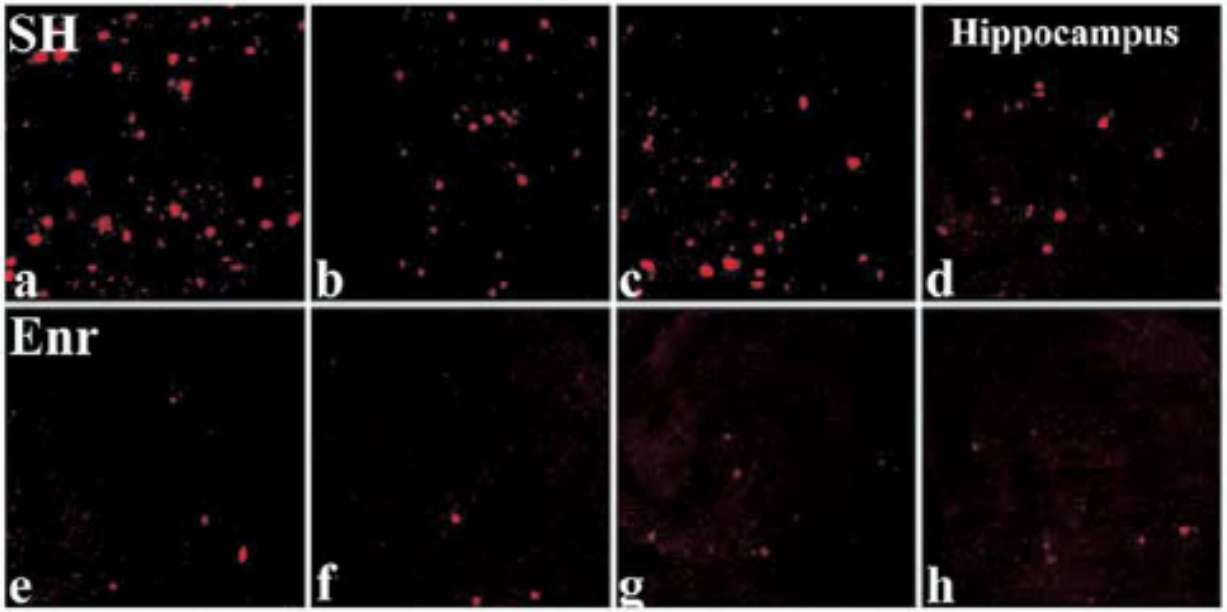


Fig. 2. Variance explained by main effects and interaction effects in 35 anxiety-related phenotypes. The x axis shows the percentage of the total variance due to the full (Full) model and to the two-locus QTL interaction term (Interaction), and the y axis the number of results obtained.

Genetic architecture of complex traits in mice

- Genetic effects are small (<5%) and they are lots of them
- The amount of epistasis depends on the phenotype
- Epistatic effects are about the same size as the main effects

Gene by environment interactions are (probably) common

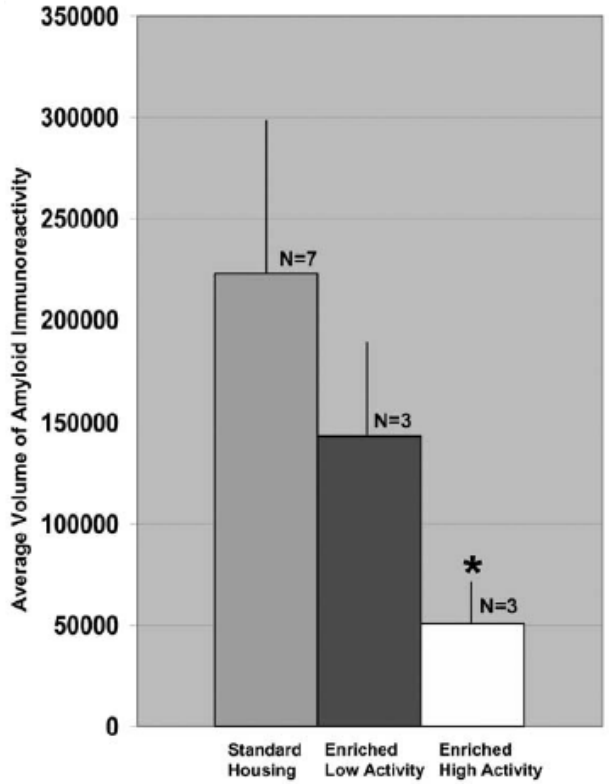


(A) Immunohistochemical analysis of brain sections of standard housing (SH, [Aa]–[Ad], hippocampus; [Ai]–[Al], cortex) and enriched mice (Enr, [Ae]–[Ah], hippocampus; [Am]–[Ap], cortex) immunolabeled with anti-Aβ 3D6 antibodies. Pictures were taken from four enriched and four standard housing mice. Scale bar, 250 μm.

Cell, Vol. 120, 701–713, March 11, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.cell.2005.01.015

Environmental Enrichment Reduces Aβ Levels and Amyloid Deposition in Transgenic Mice

Gene by environment interactions are (probably) common



Cell, Vol. 120, 701–713, March 11, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.cell.2005.01.015

Environmental Enrichment Reduces Aβ Levels and Amyloid Deposition in Transgenic Mice

Genotype–environment interactions in mouse behavior: A way out of the problem

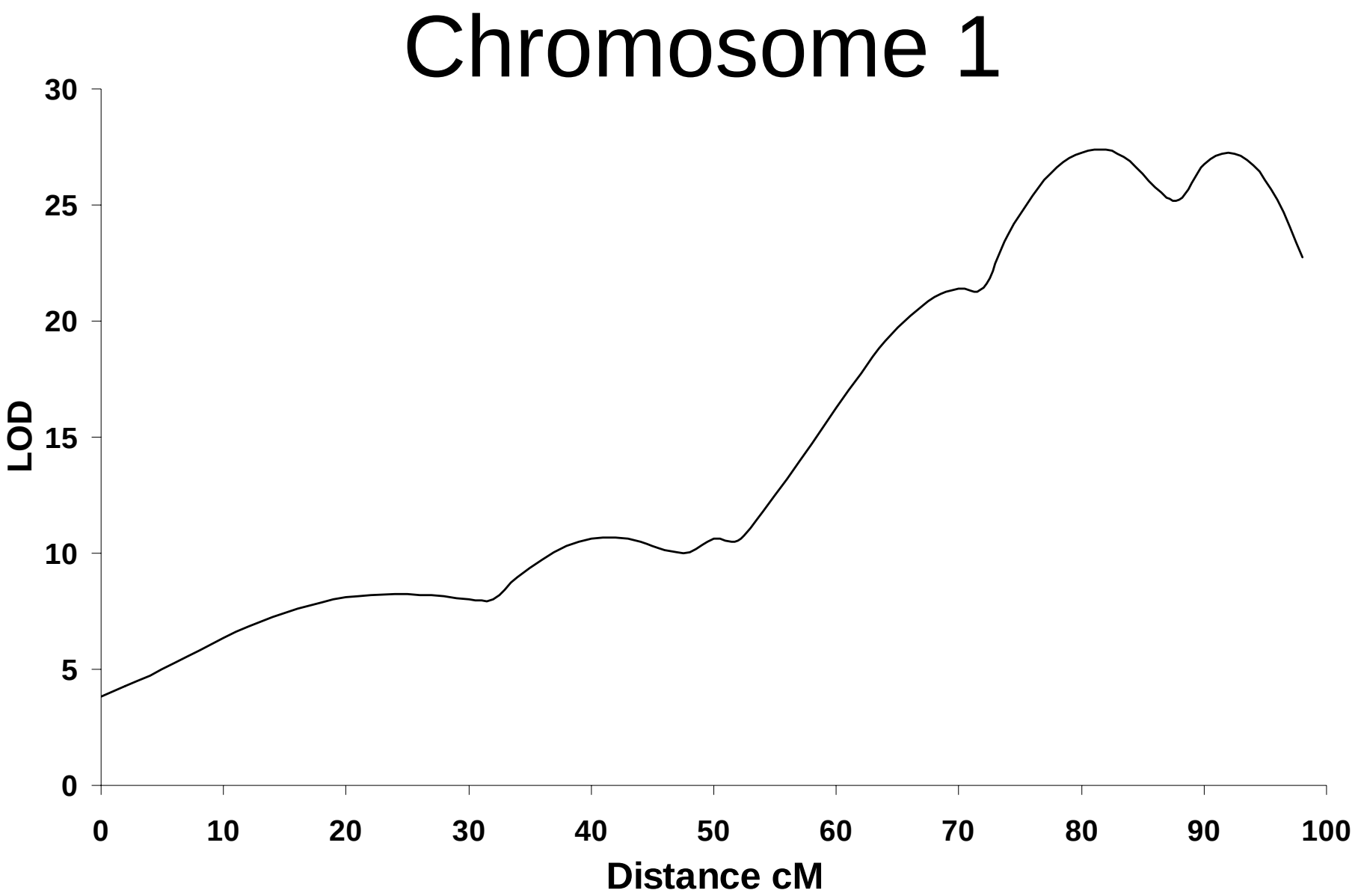
Neri Kafkafi*†‡, Yoav Benjamini†§, Anat Sakov§, Greg I. Elmer*, and Ilan Golani¶

*Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD 21228; and §Department of Statistics and Operations Research, The Sackler Faculty of Exact Sciences, and ¶Department of Zoology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv 69978, Israel

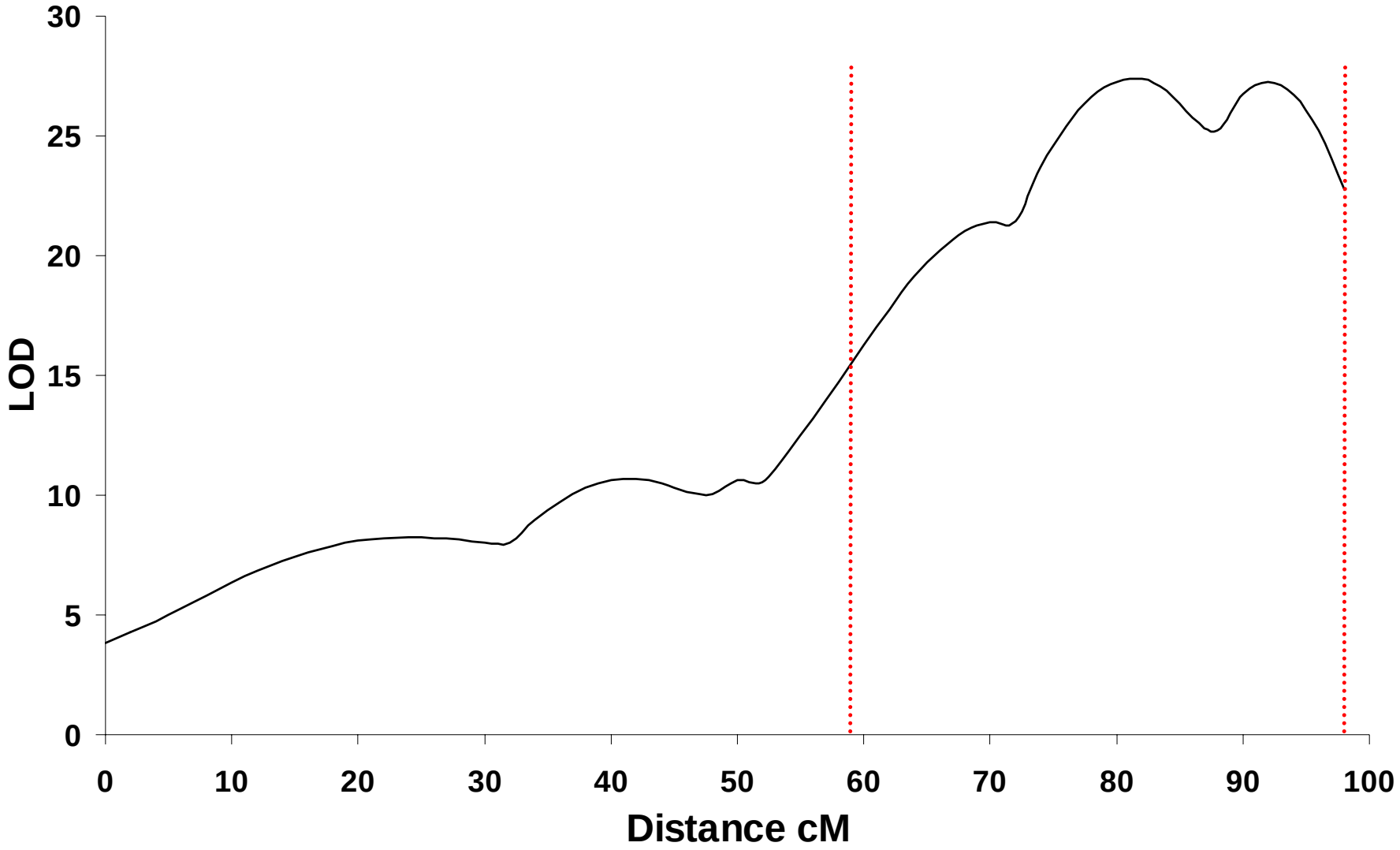
PNAS | March 22, 2005 | vol. 102 | no. 12 | 4619–4624

Genetic architecture of complex traits in mice

- Genetic effects are small (<5%) and they are lots of them
- The amount of epistasis depends on the phenotype
- Epistatic effects are about the same as main effects
- Gene by environment interactions are probably common (in knock-outs)


Chromosome 1
LOD
30
25
20
15
10
5
0
0
10
20
30
40
50
60
70
80
90
100
Distance cM

Chromosome 1



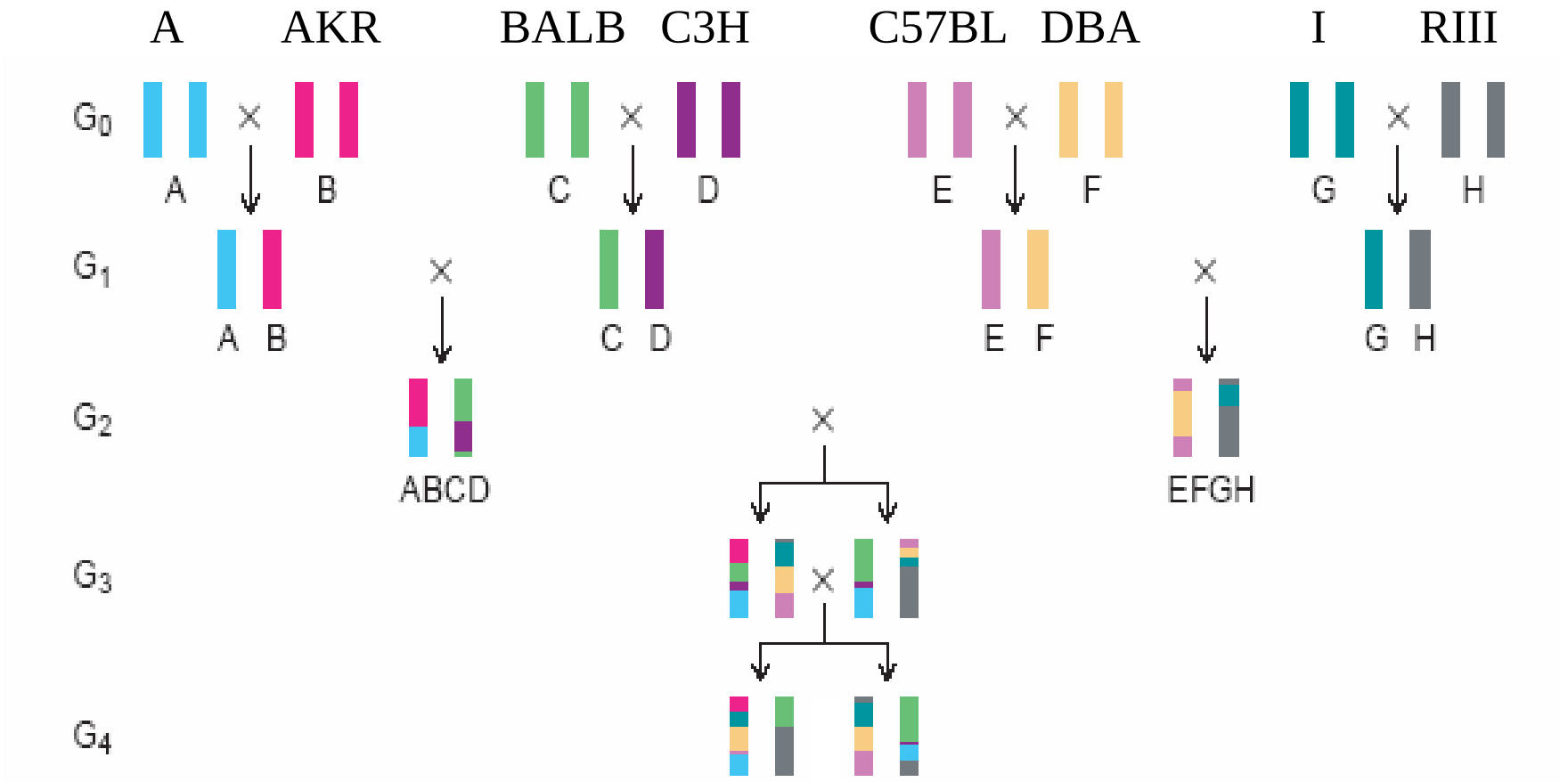
Genetic architecture at high resolution

- Mapping in outbreds: heterogeneous stock
- Mapping in outbreds: MF1
- Gene knockout/QTL interaction test

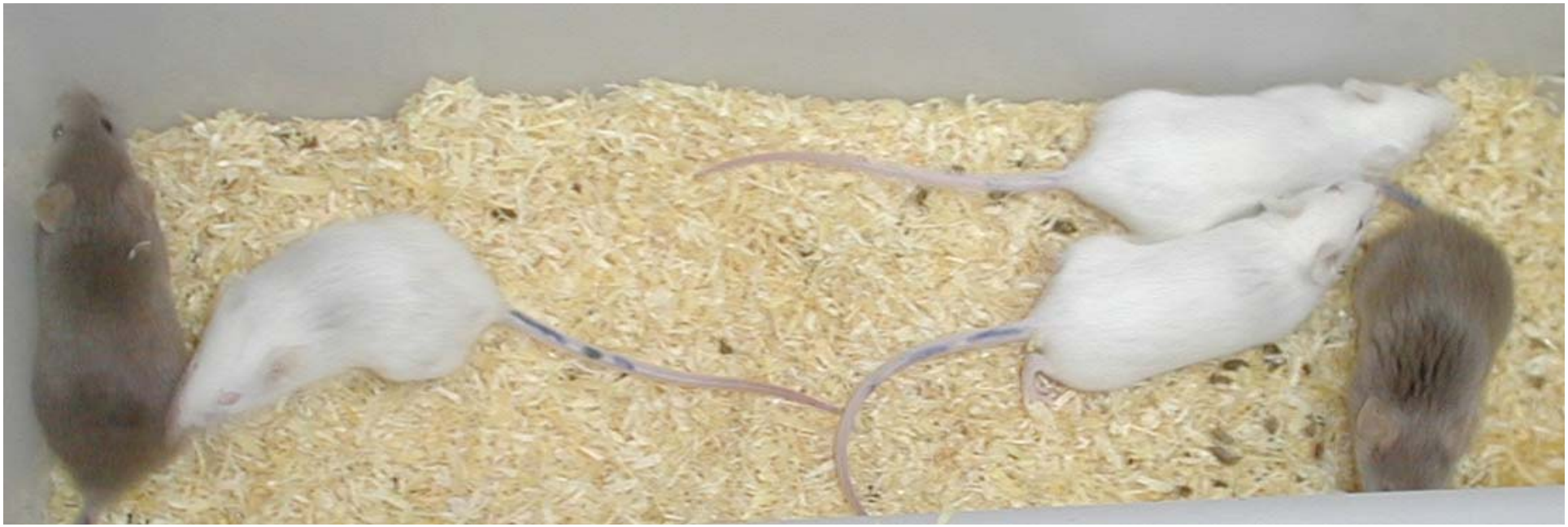
Genetically Heterogeneous Mice

A AKR BALB C3H C57BL DBA I RIII

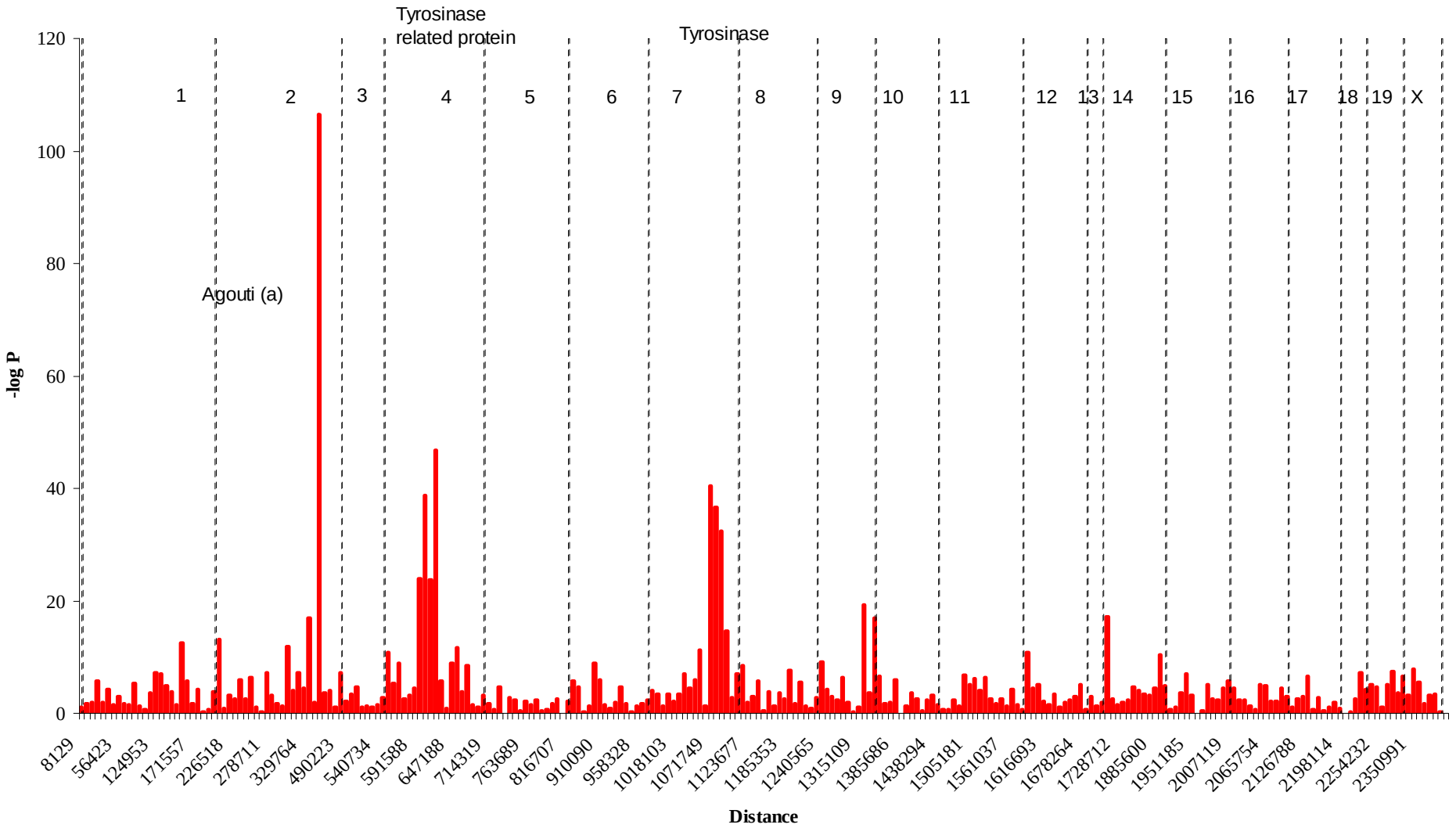
HS provide increased mapping resolution



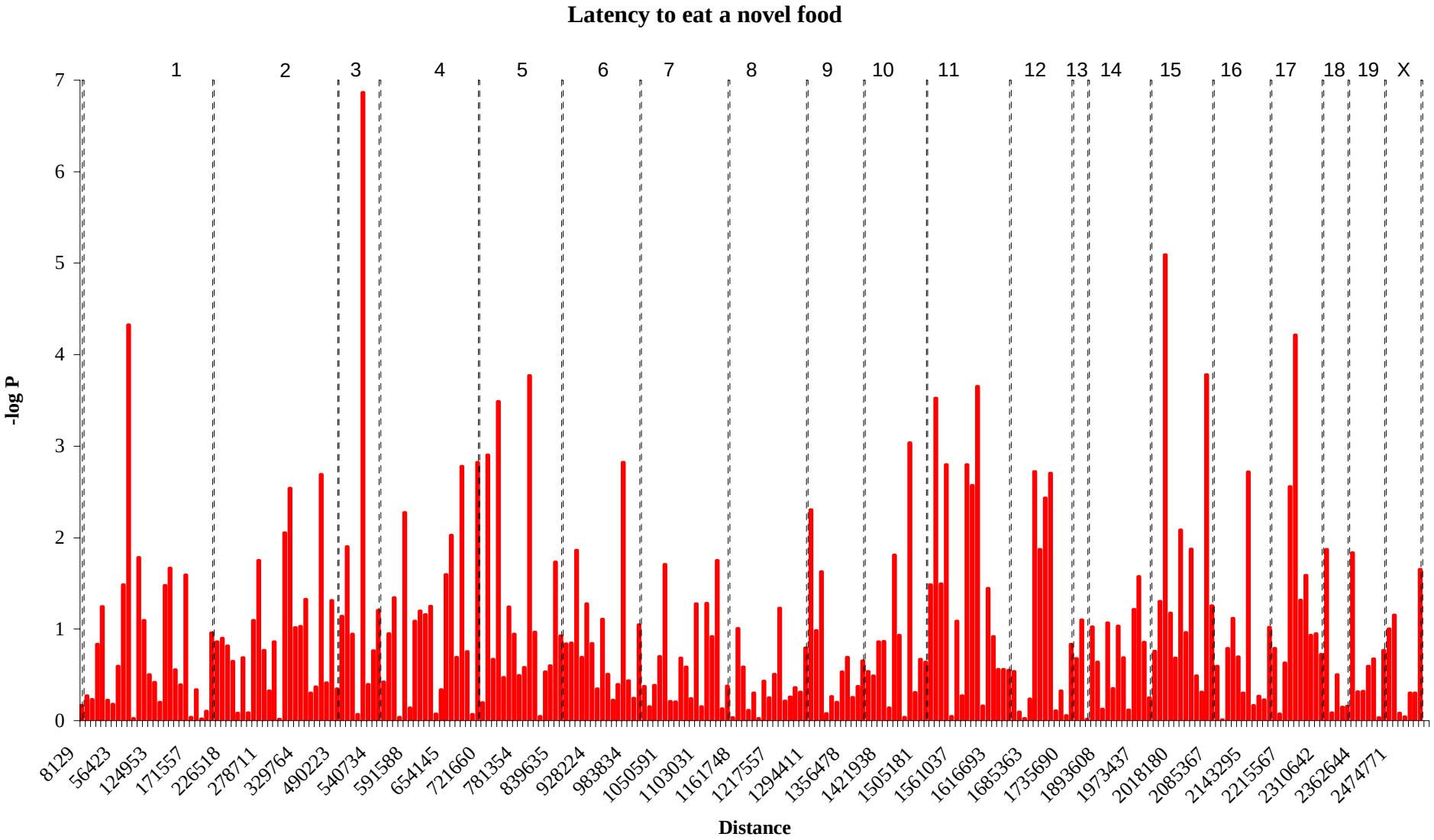
Genetically Heterogeneous Mice



Coat Color


Tyrosinase related protein
Tyrosinase
Agouti (a)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
-log P
120
100
80
60
40
20
0
8129
56423
124953
171557
226518
278711
329764
490223
540734
591588
647188
714319
763689
816707
910090
958328
1018103
1071749
1123677
1185353
1240565
1315109
1385686
1438294
1505181
1561037
1616693
1678264
1728712
1885600
1951185
2007119
2065754
2126788
2198114
2254232
2350991
Distance

Behavior


Latency to eat a novel food
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
-log P
0
1
2
3
4
5
6
7
8129
56423
124953
171557
226518
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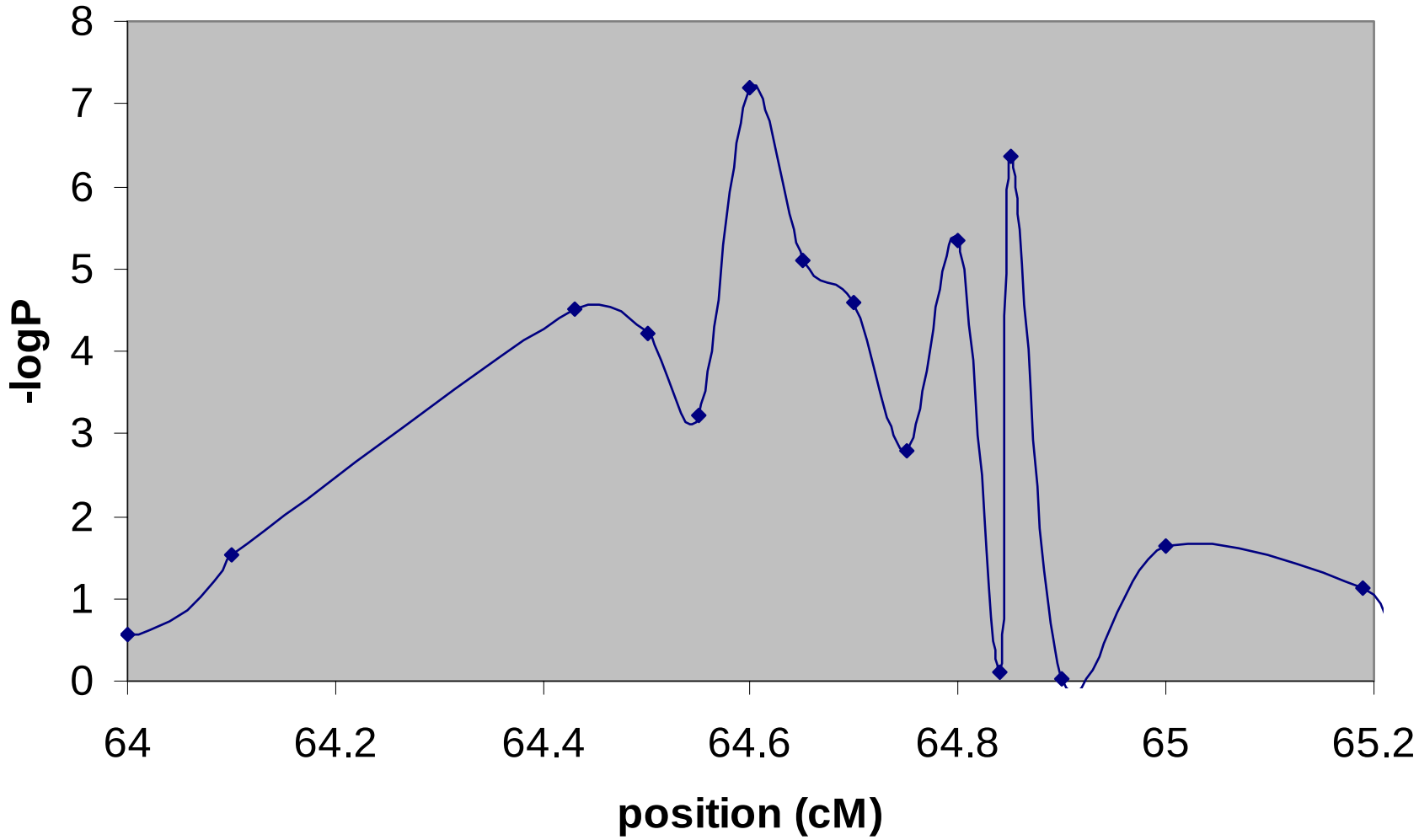
1103031
1161748
1217557
1294411
1356478
1421938
1505181
1561037
1616693
1685363
1735690
1893608
1973437
2018180
2085367
2143295
2215567
2310642
2362644
2474771
Distance

High resolution mapping (anxiety phenotype, chromosome 1)



Single marker mapping

Marker	Position (cM)	- LogP	Allele Size (bp)
D1Mit423	64.84	6.4	127
			135
D1Mit496	64.85	0.1	117
			122

Progenitor strain origin of alleles


A


AKR


BALB


C3H


C57BL


DBA


I

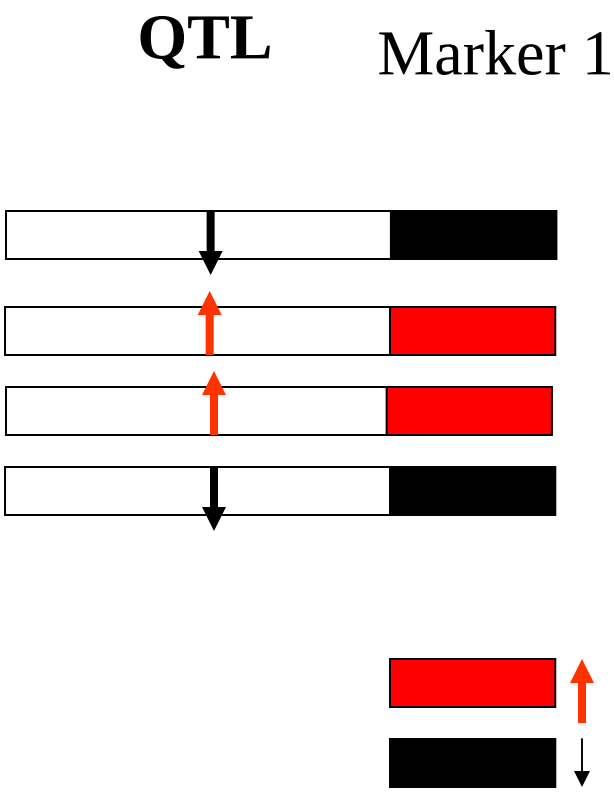

RIII

LogP								
6.4	135	127	127	135	127	127	127	127

Progenitor strain origin of alleles

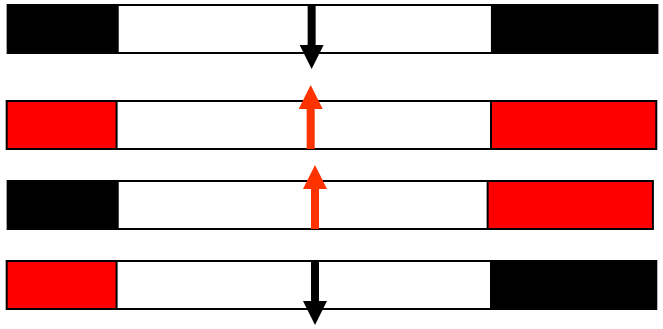
	A	AKR	BALB	C3H	C57BL	DBA	I	RIII
LogP								
6.4	135	127	127	135	127	127	127	127
0.1	117	117	122	117	122	122	117	122

Relation Between Marker and Genetic Effect



Relation Between Marker and Genetic Effect

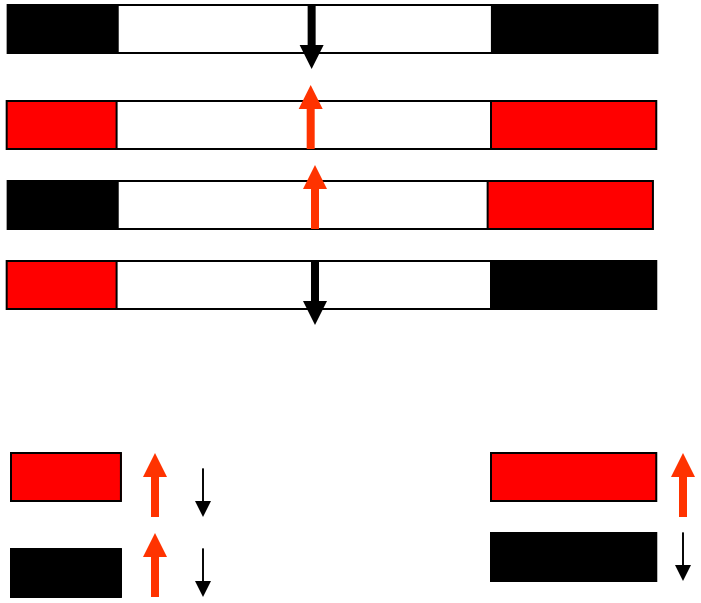
Marker 2 **QTL** Marker 1



Observable effect

Relation Between Marker and Genetic Effect

Marker 2 **QTL** Marker 1



No effect observable

Observable effect

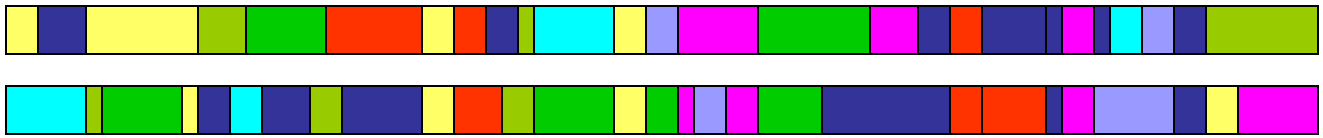
Strain distribution pattern indicates QTL action

BALB/c, C57BL/6, DBA/2, RIII, I, AKR ↓ Low anxiety

A/J, C3H ↑ High anxiety

Observed chromosome structure

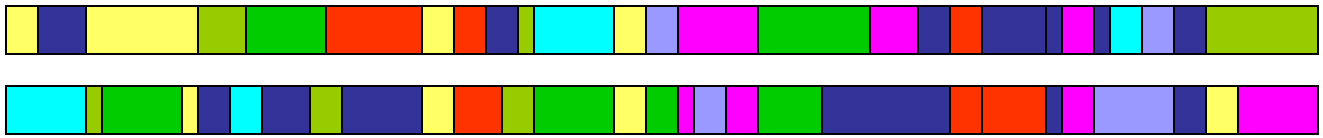
Hidden Chromosome Structure

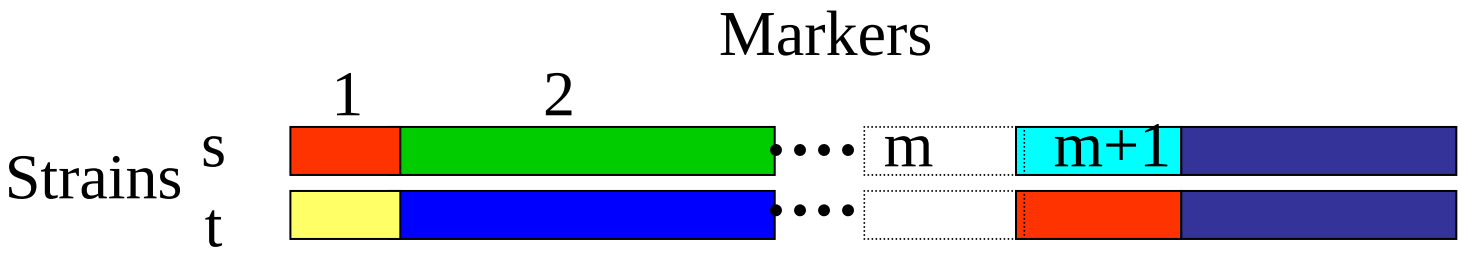


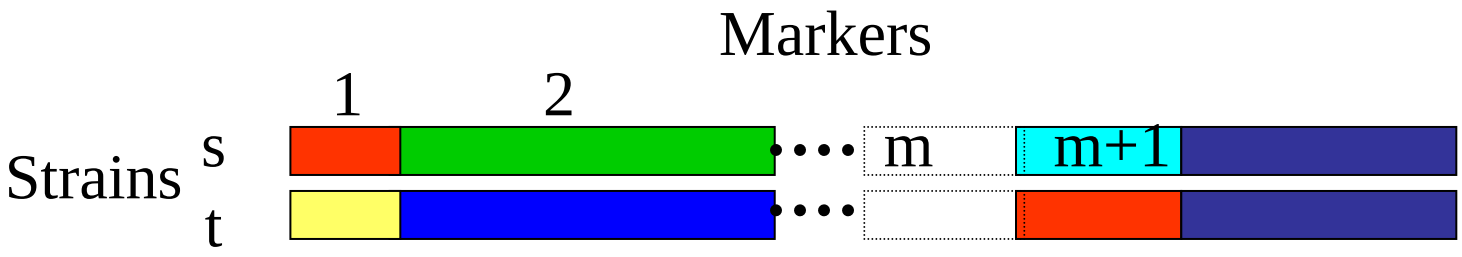
Calculate the probability that an allele descends from each progenitor

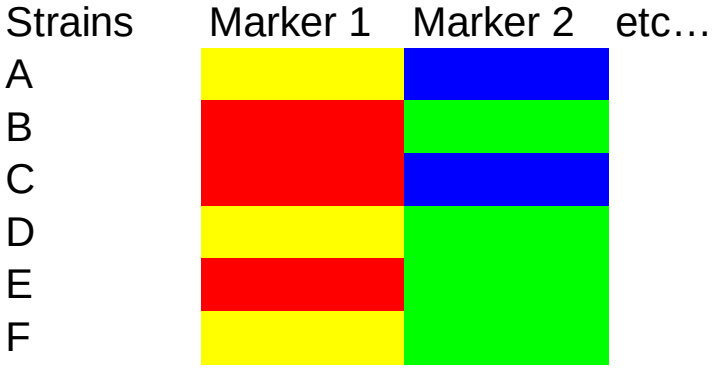
Observed chromosome structure

Hidden Chromosome Structure




Markers
1
2
Strains
s
t
m
m+1


Markers
1
2
Strains
s
t
m
m+1

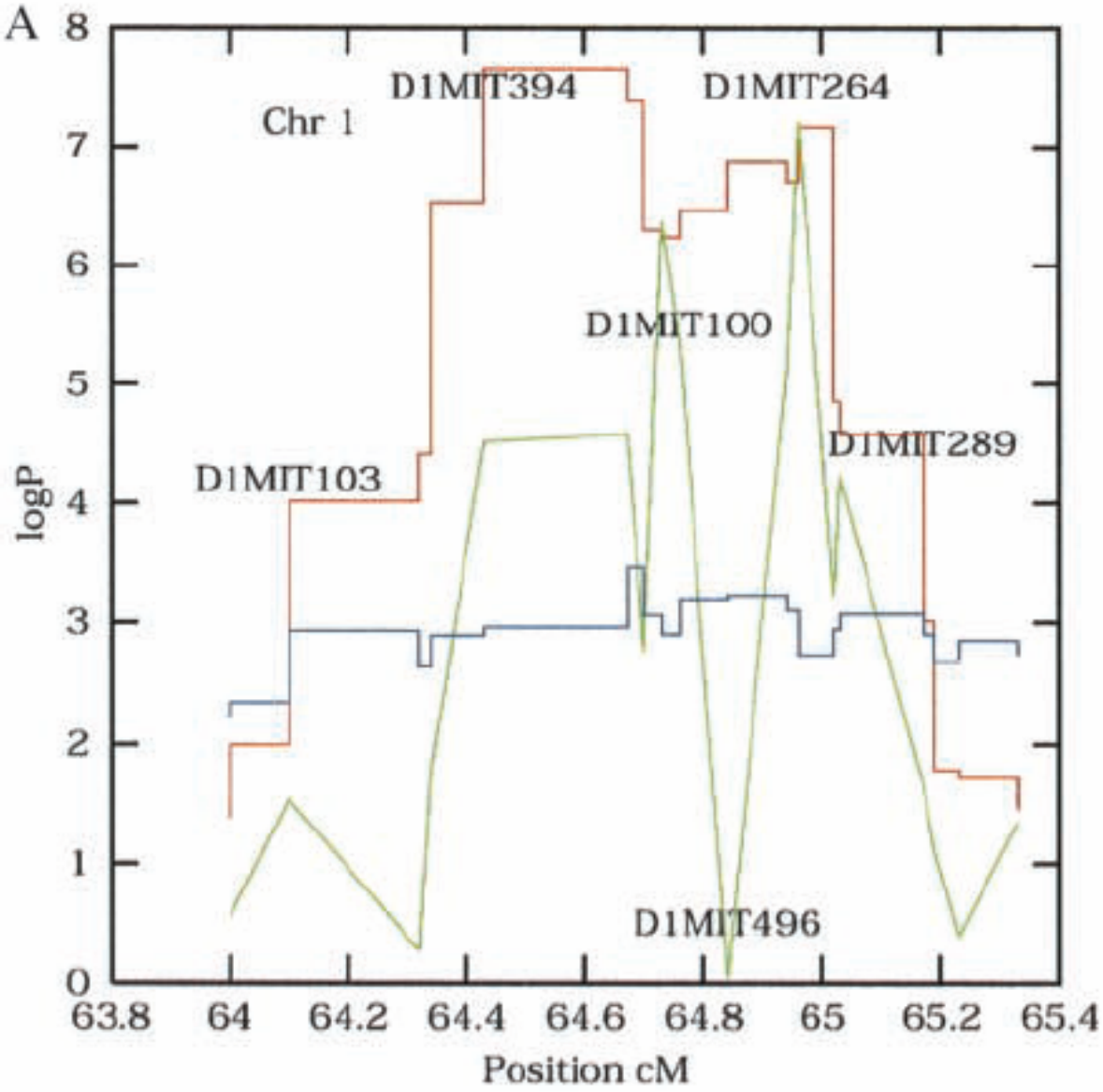

Strains
Marker 1
Marker 2
etc…
A
B
C
D
E
F

Analysis

$$x_m(s,t) = \sum_{s',t'} x_{m-1}(s',t')\psi_m(s,t|s',t')$$

Probabilistic Ancestral Haplotype Reconstruction (descent mapping): implemented in HAPPY

http://www.well.ox.ac.uk/~rmott/happy.html


A
Chr 1
D1MIT394
D1MIT264
D1MIT100
D1MIT289
D1MIT103
D1MIT496
logP
Position cM
0
1
2
3
4
5
6
7
8
63.8
64
64.2
64.4
64.6
64.8
65
65.2
65.4

Gene identification

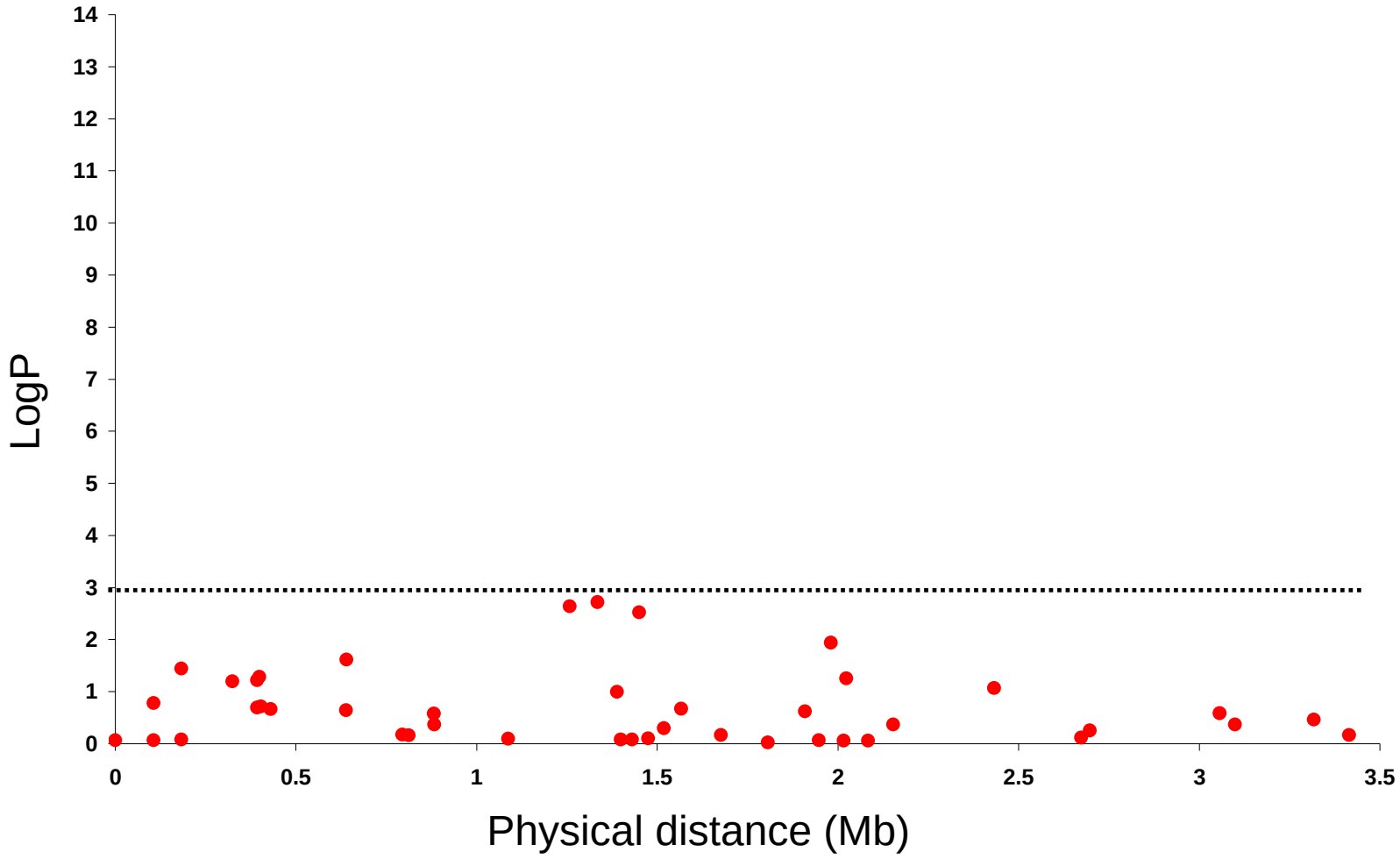
- Mapping in outbreds: heterogeneous stock
- Mapping in outbreds: MF1
- Gene knockout/QTL interaction test

MF1 Mice

Genetic analysis of MF1 outbred mice

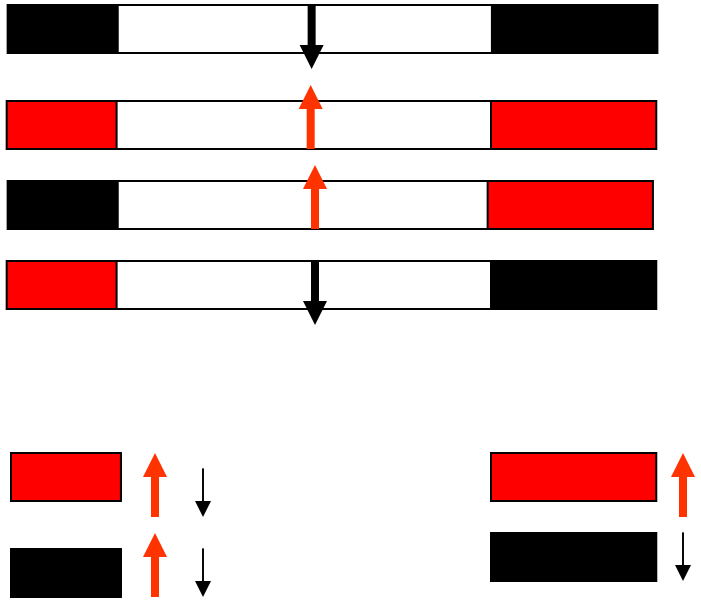
- Single marker association

Single Marker Analysis



Relation Between Marker and Genetic Effect

Marker 2 **QTL** Marker 1



No effect observable

Observable effect

Unknown progenitors

- Sometime in the 1970's….

LACA x CF

↓

↓

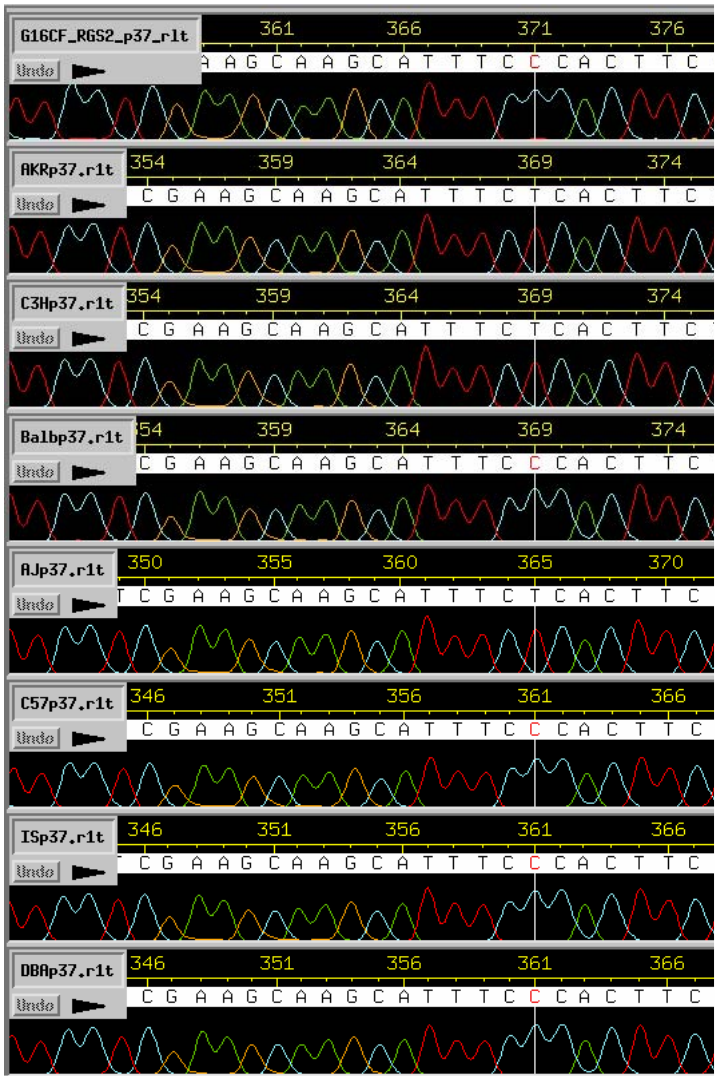
↓

MF1

SNP

MF1

Inbred strains



MF1 haplotype reconstruction

- Genotype 42 SNPs across QTL in 729 MF1 mice
- Construct haplotypes
- Reconstruct descent of each haplotype using inbred strains as theoretical progenitors

Haplotypes derived from inbred strains

11111111111177777777777777777777777777777777

22222333333333333333333333333333333333331111

66666666633333333333333333333333333333331111

11111111333111113333333333333333333331111666

11111111333333333333333333333333333333331111

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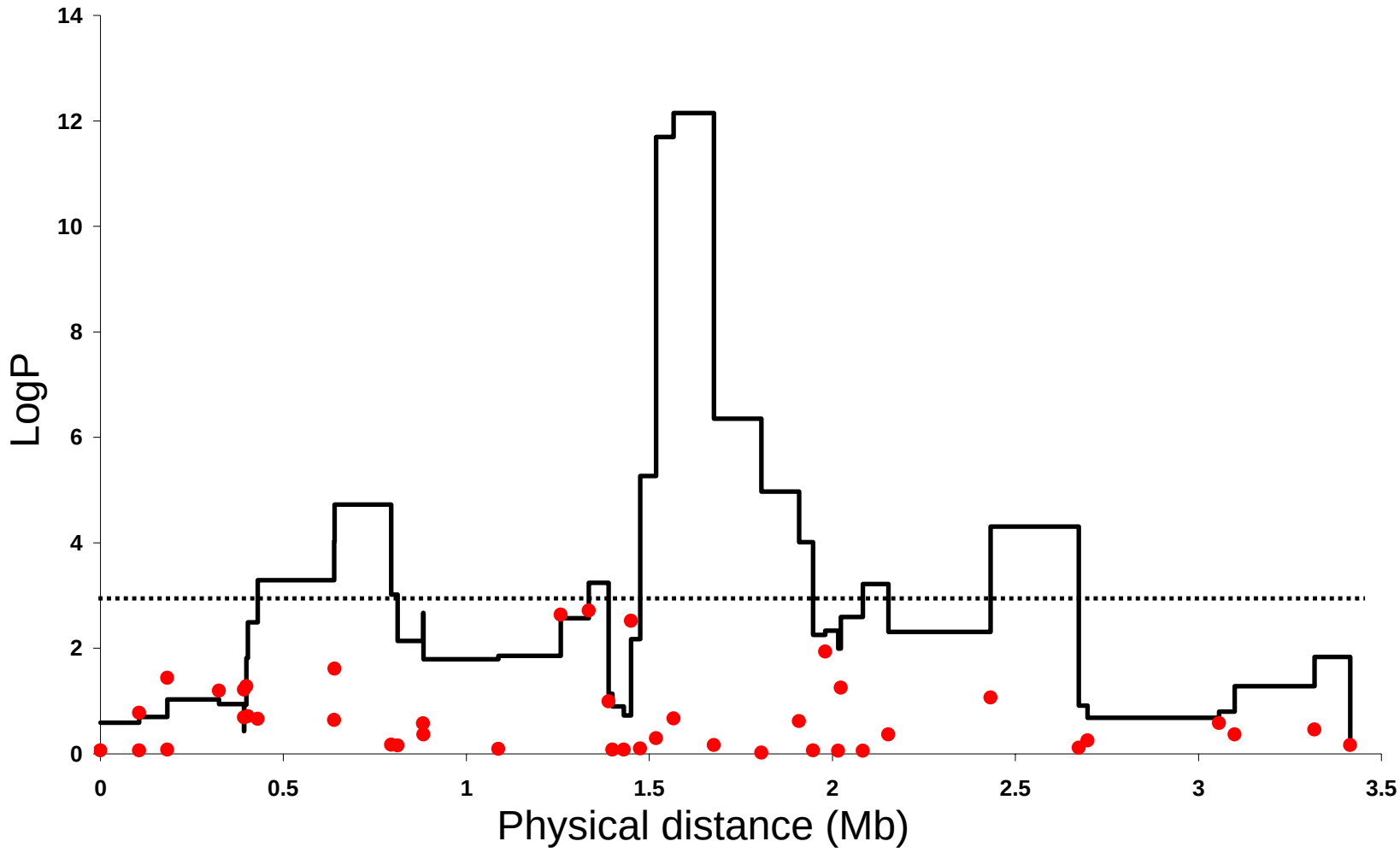
Mapping by descent



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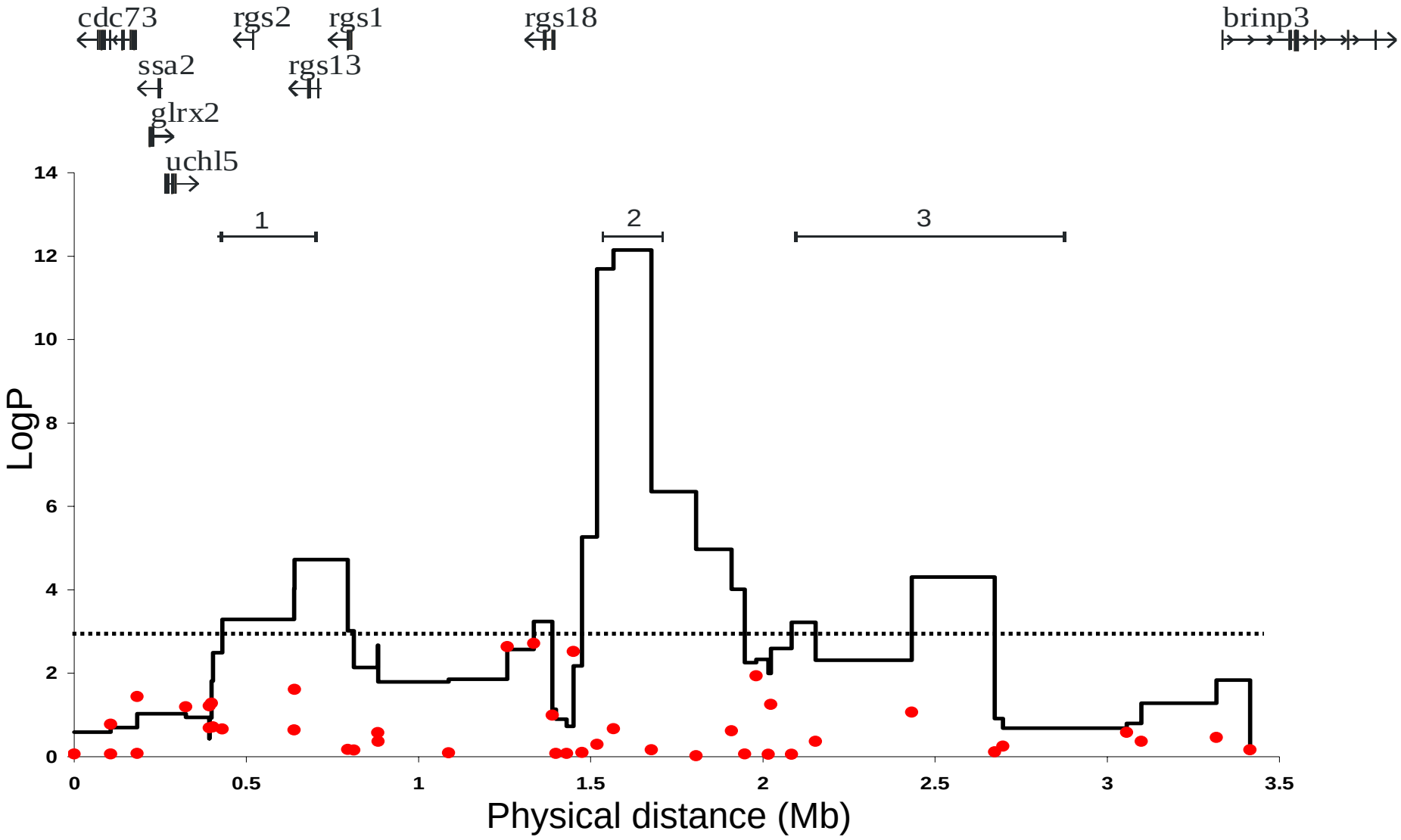

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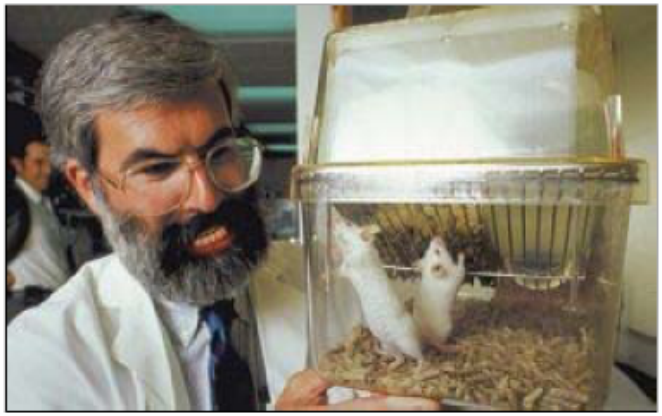
VOLUME 40 ISSUE 49 AMERICA'S FINEST NEWS SOURCE™ 8 DECEMBER 2004

SCIENCE

World's Scientists Admit They Just Don't Like Mice

ZURICH, SWITZERLAND—Nearly 700 scientists representing 27 countries convened at the University of Zurich Monday to formally announce that their experimentation on mice has been motivated not by a desire to advance human knowledge, but out of sheer distaste for the furry little rodents.



Above: White examines detested specimens in his Oxford lab.

"As a man of science, I deal with facts, and the fact is that mice are gross," said Dr. Douglas White, chair of the Oxford biogenetics department and lifelong mouse-hater. "They're squirmy, scurrying little vermin, and they make my skin crawl. I speak for all of my assembled colleagues when I say that the horrible little things deserve the worst we can dish out."

According to a 500-word statement, scientists hate mice for "their beady little eyes," "their repulsive tails," and "the annoying little squeaking sounds they make."

At the press conference, several scientists detailed their involvement in the centuries-long ruse of "conducting experiments" and "curing diseases."

"For years, I've used lab mice to research cell breakdown in living tissue—and I've been lucky enough to make some pretty important medical advancements along the way," said researcher Ellen Gresham of the Harvard Institute for Advanced Studies. "But even if there were no scientific benefit to the work I do, I'd still experiment on mice, just to watch them suffer."

"The truth is, mice are particularly ill-suited for our tissue study," Gresham added. "We could construct a computer model that would yield more accurate results, but we don't care."

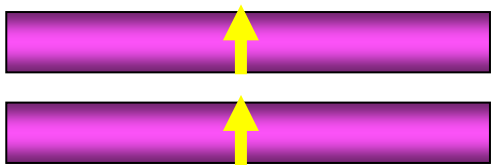
According to Gresham, scientists have enjoyed dissolving mice in acid, spinning them in centrifuges, blowing them up in vacuum chambers, and forcing them to navigate exit-free mazes for years—all the while towering above them, laughing.

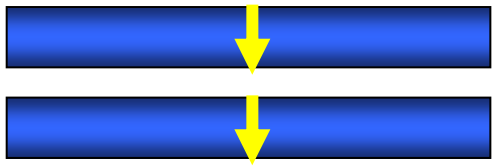
Gene identification

- Quantitative complementation/QTL-knockout interaction test

Quantitative Complementation

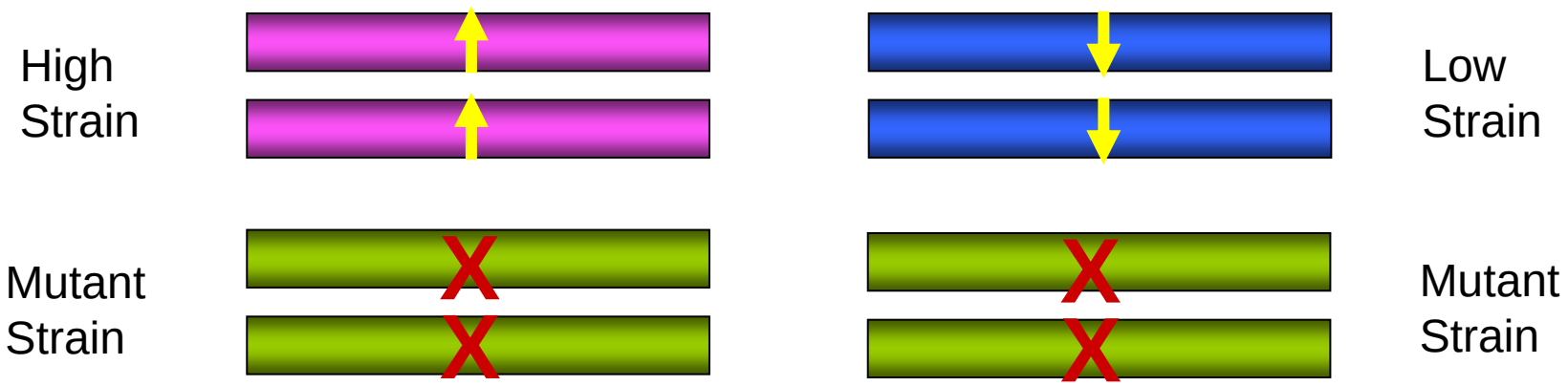
High strain



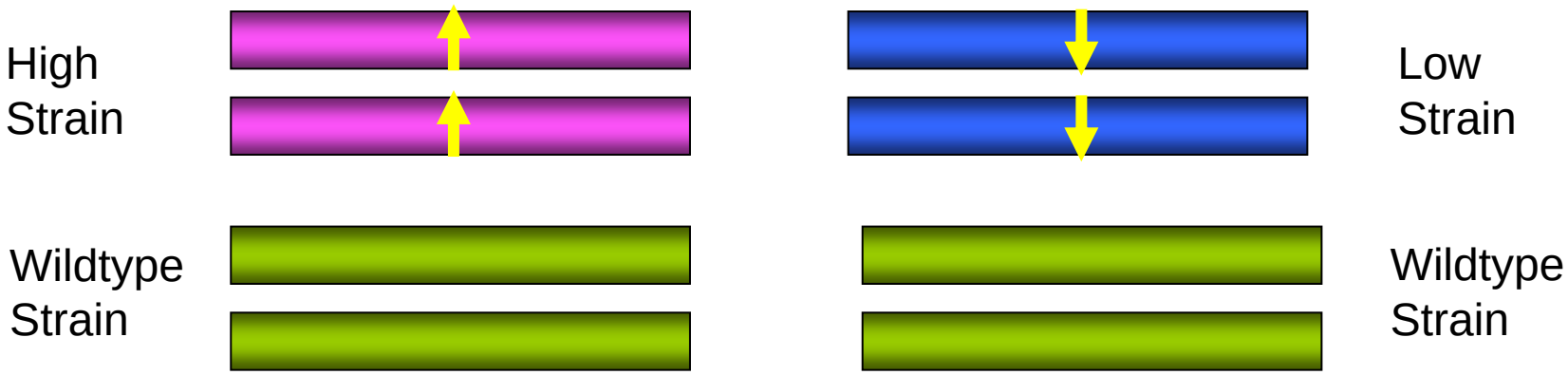


Low strain

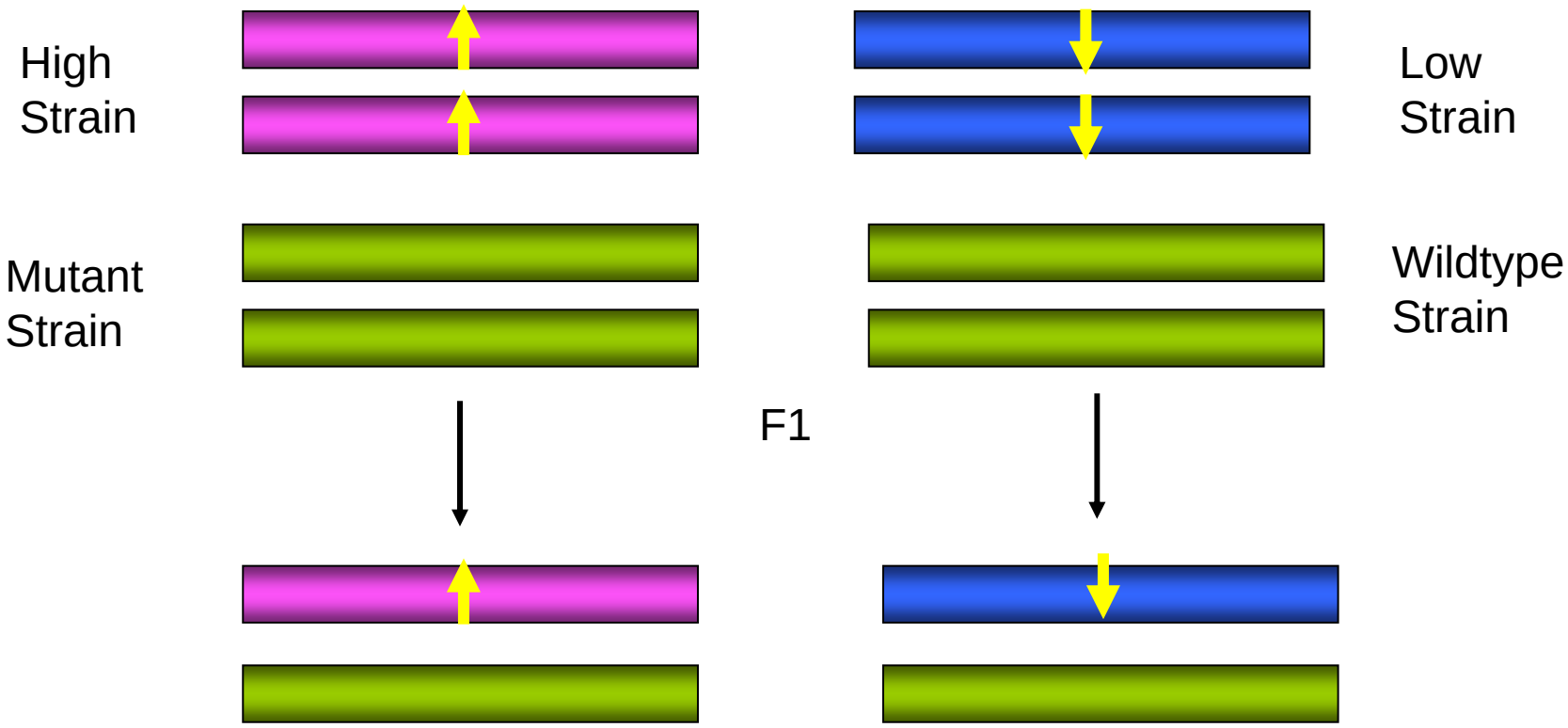
Quantitative Complementation



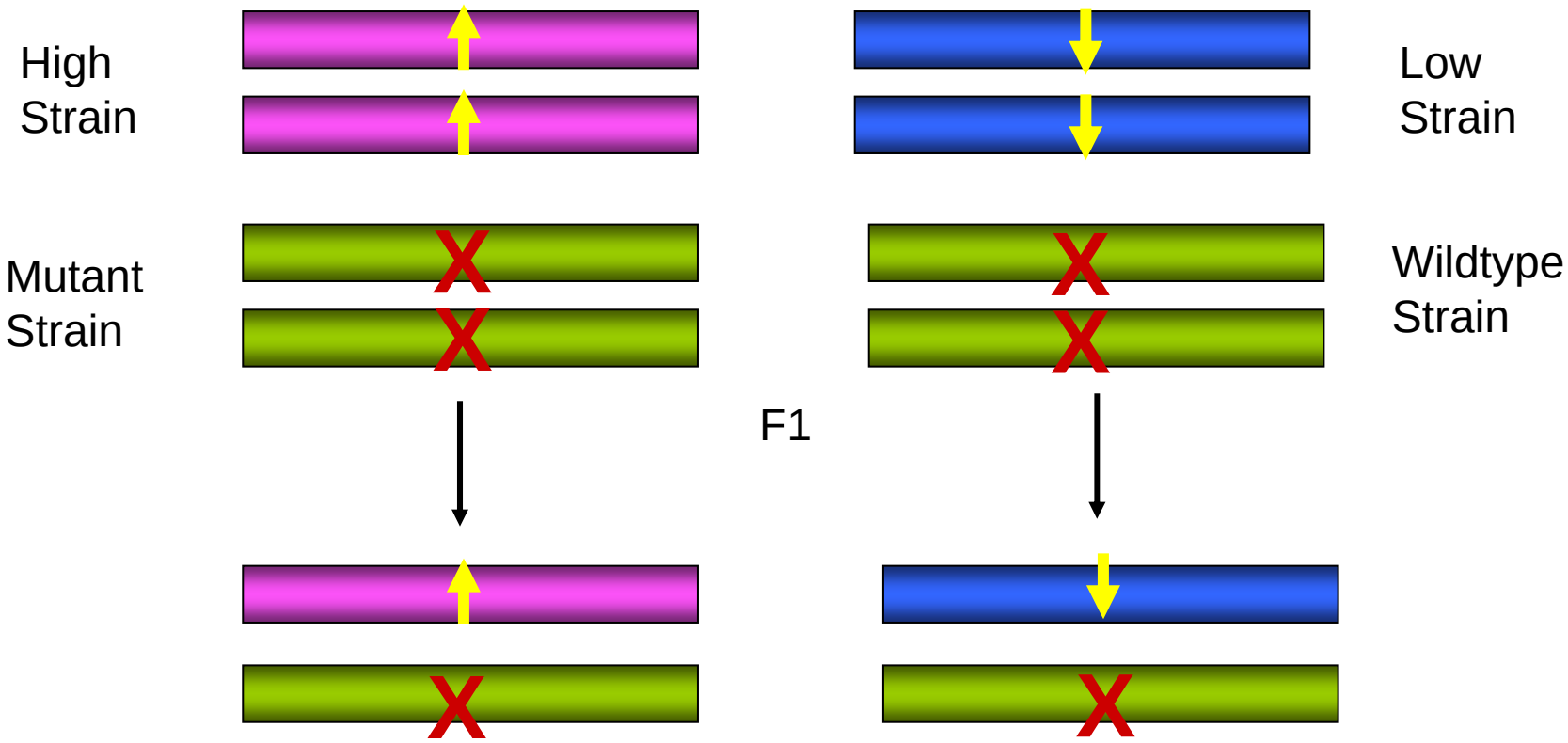
Quantitative Complementation



Quantitative Complementation



Quantitative Complementation



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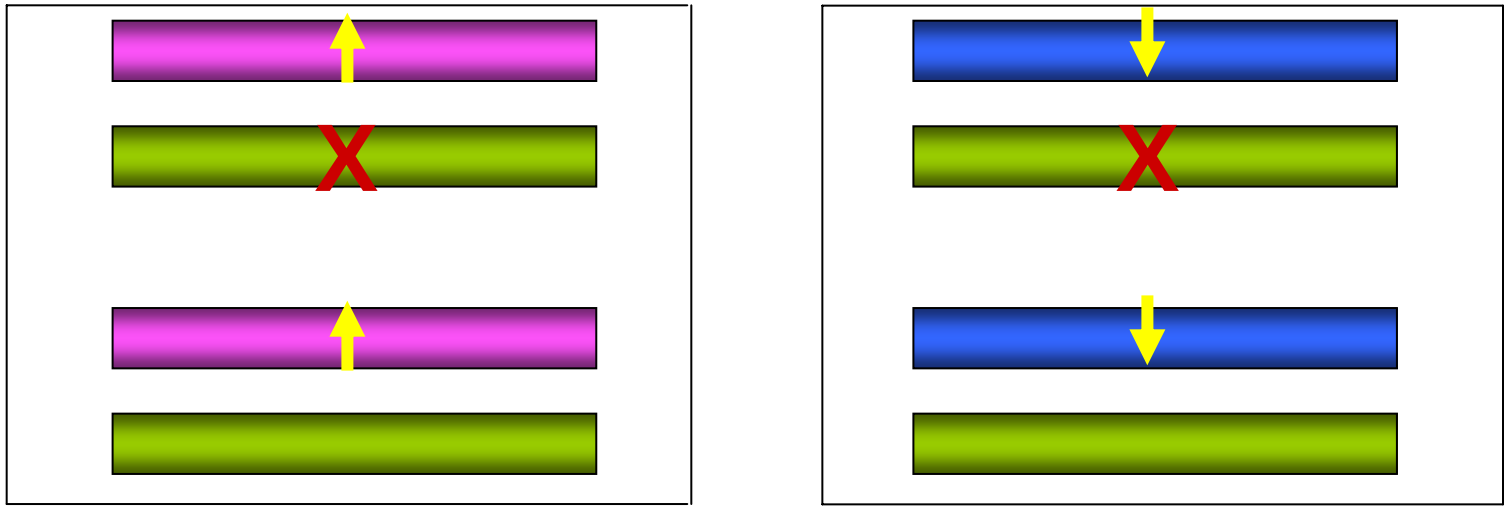
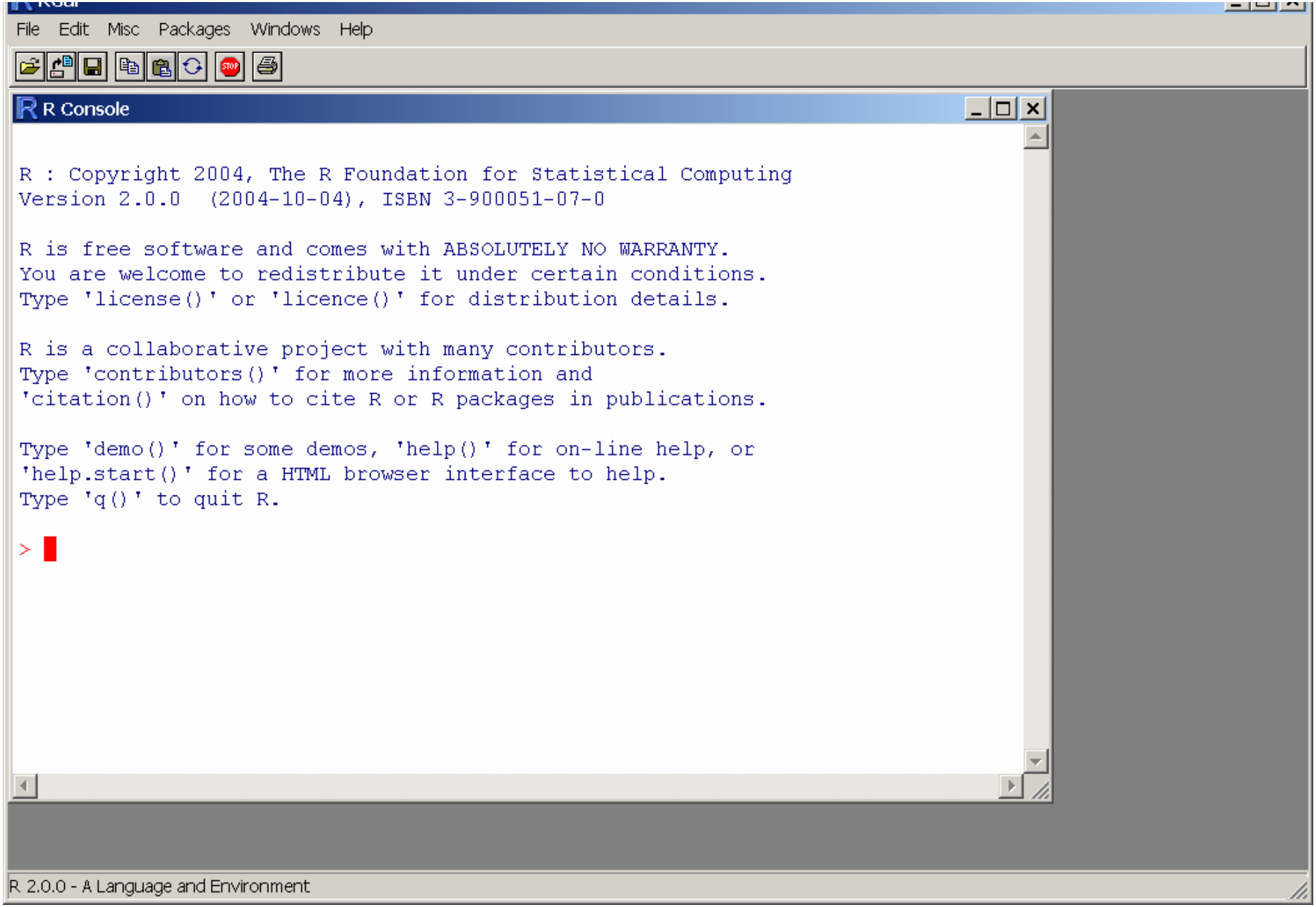


```
> fit <- lm( Phenotype ~ Cross * Background )
> anova(fit)
```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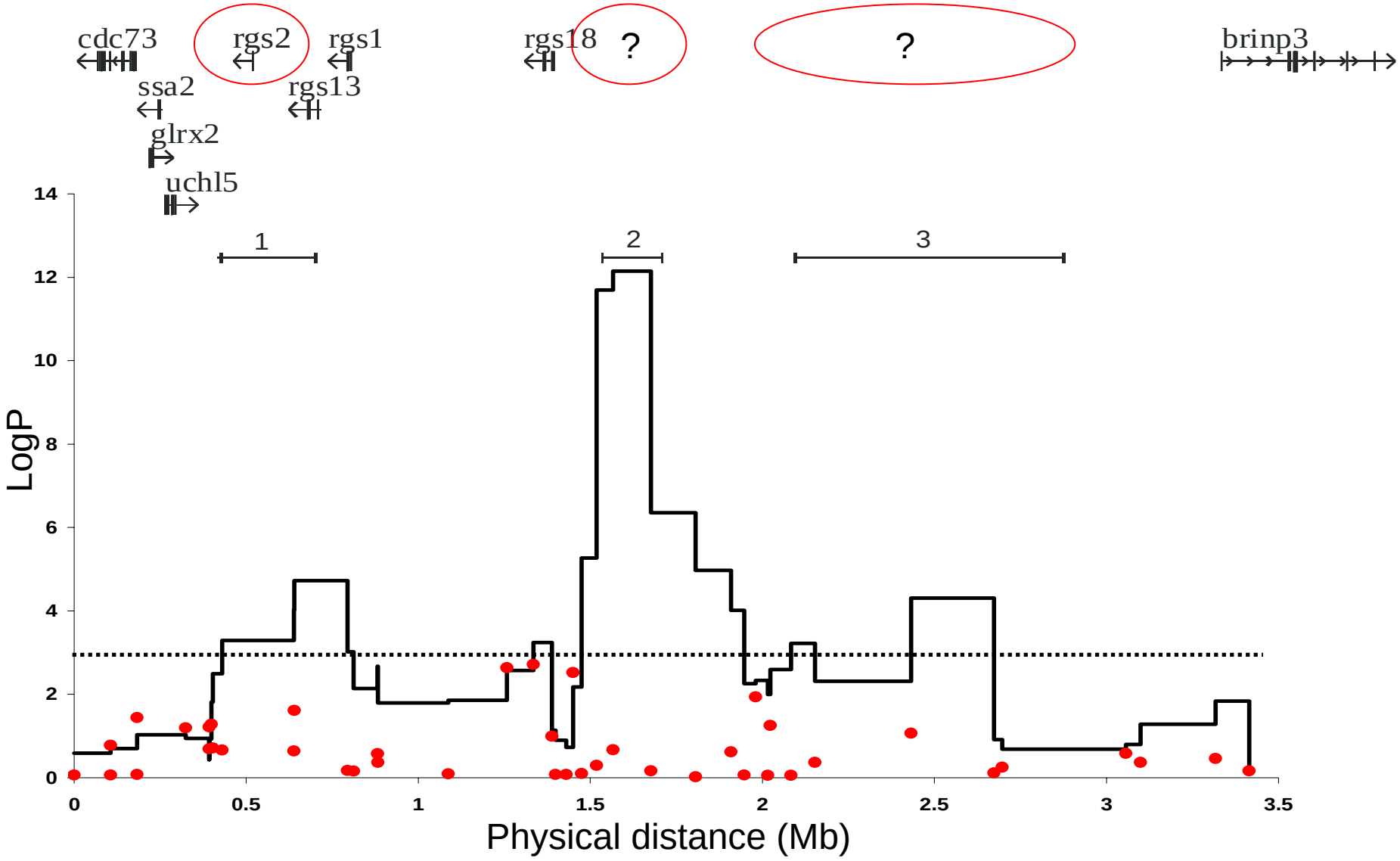
'help.start()' for a HTML browser interface to help.
Type 'q()' to quit R.
>
R 2.0.0 - A Language and Environment

Quantitative complementation

C3H

	P-value	# animals
OFA		92
Background	0.246	
Cross	0.011	
Background:Cross	**0.003**	

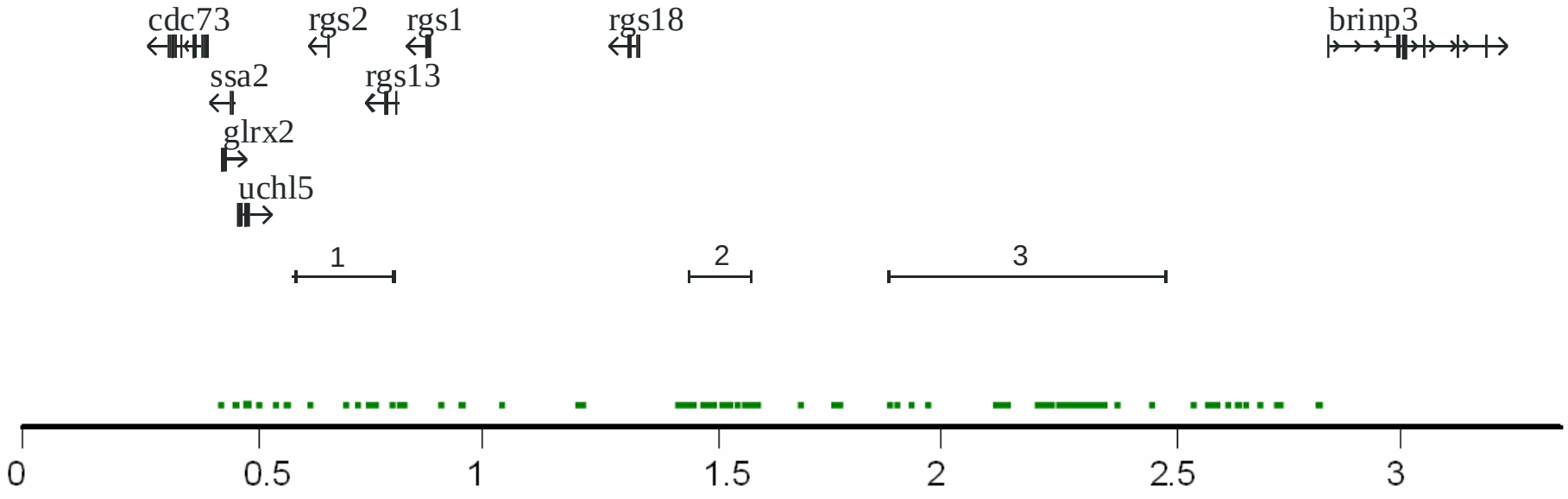
Mapping by descent



Genetic architecture of complex traits in mice

- Genetic effects are small (<5%) and they are lots of them
- The amount of epistasis depends on the phenotype
- Epistatic effects are about the same as main effects
- The molecular basis of complex traits can lie in non-coding sequence

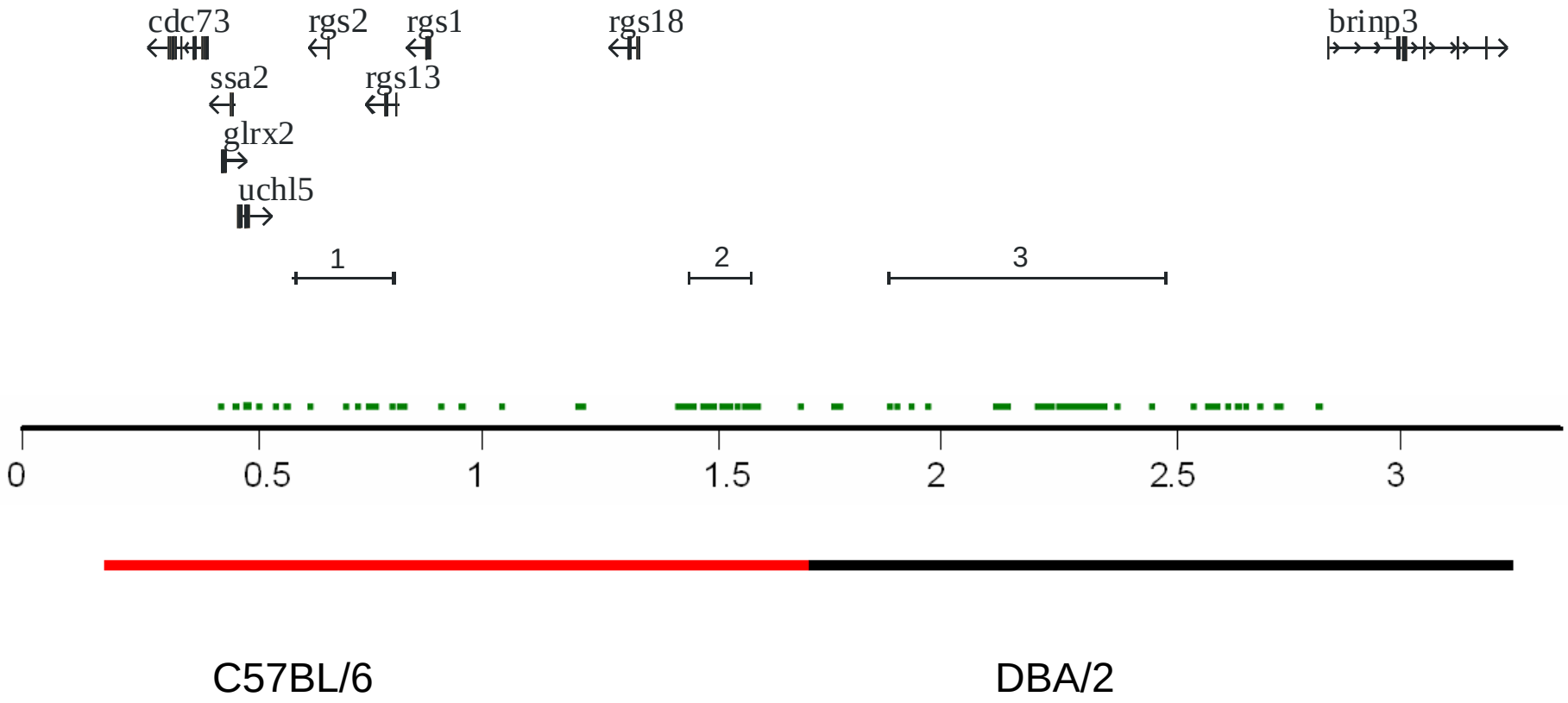
Sequence of KO strain



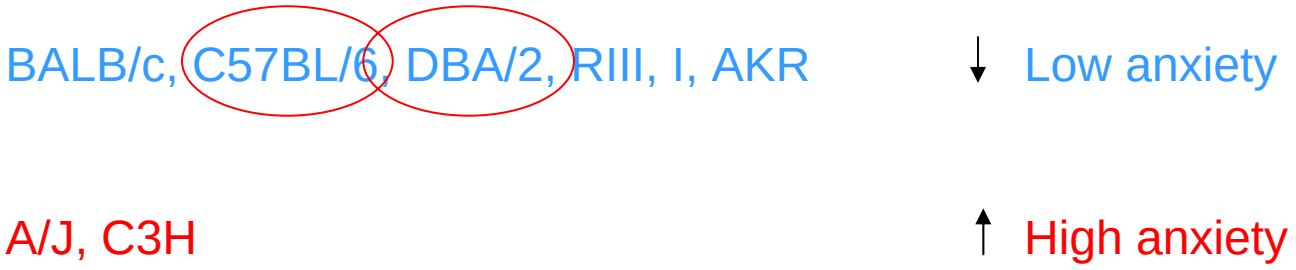
		B6129P2_RGS2	C57	AKR	RIII	Balb/c	C3H	DBA	AJ	I
CNS1908023	198	C	C	C	T	C	C	C	C	C
CNS1908023	206	T	T	T	A	T	T	T	T	T
CNS1908023	260	A	A	A	G	A	A	A	A	A
CNS1908023	280	T	T	T	G	T	T	T	T	T
CNS1908023	284	A	A	A	G	A	A	A	A	A
CNS1908023	307	T	T	T	G	T	T	T	T	T
CNS1908023	349	C	C	C	T	C	C	C	C	C
CNS1908023	356	A	A	A	T	A	A	A	A	A

		B6129P2_RGS2	C57	AKR	RIII	Balb/c	C3H	DBA	AJ	I
LD2_1139945	480	T	C	T	T	C	C	T	C	T
LD2_1139945	546	G	C	G	G	C	C	G	C	G
LD2_1139945	607	G	A	G	G	A	A	G	A	G
LD2_1139945	672	T	C	T	T	C	C	T	C	T
LD2_1139945	688	C	T	C	C	T	T	C	T	C

Sequence of KO strain



Strain distribution pattern of QTL



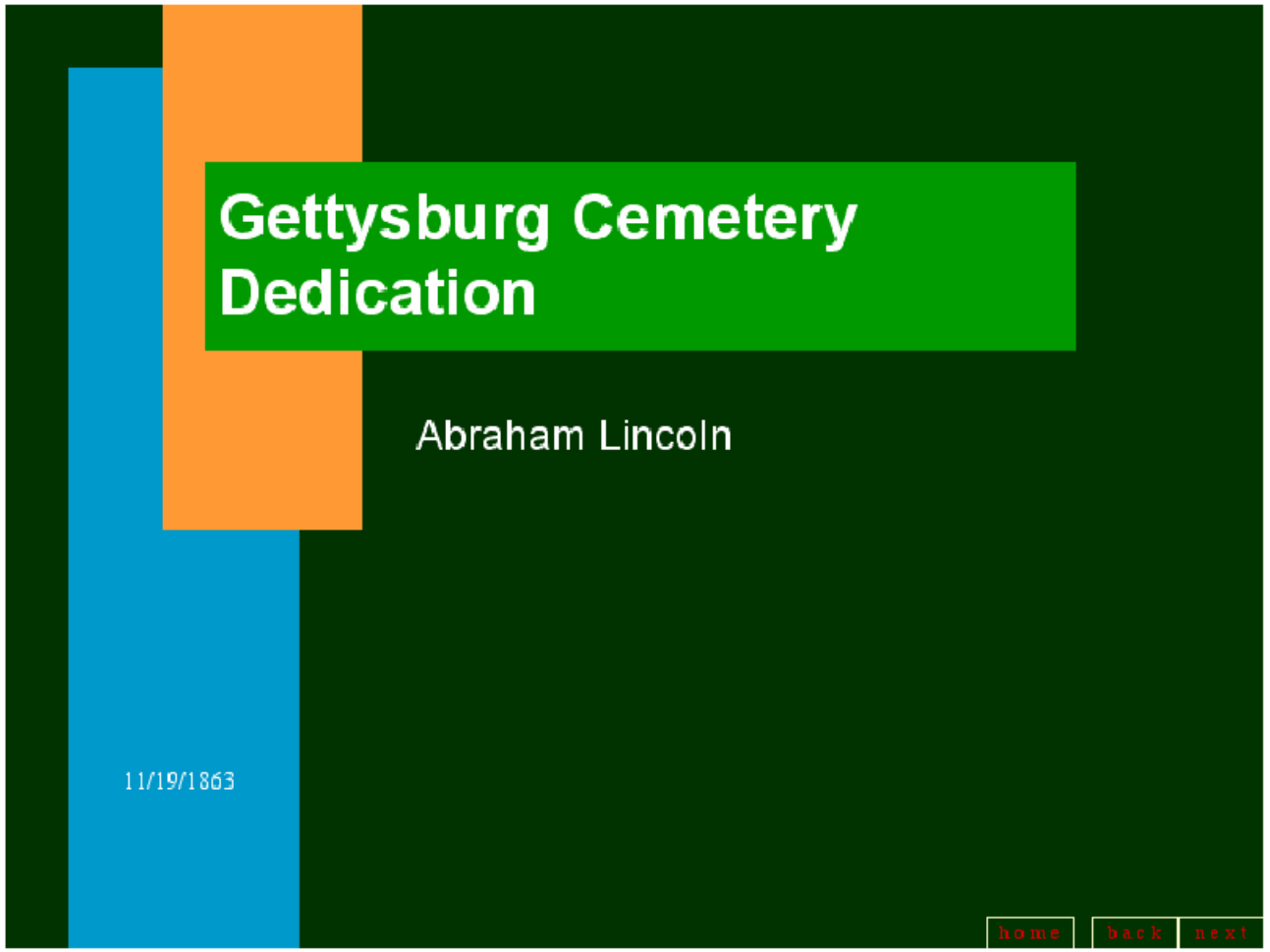
QTL-Knockout interaction

C3H

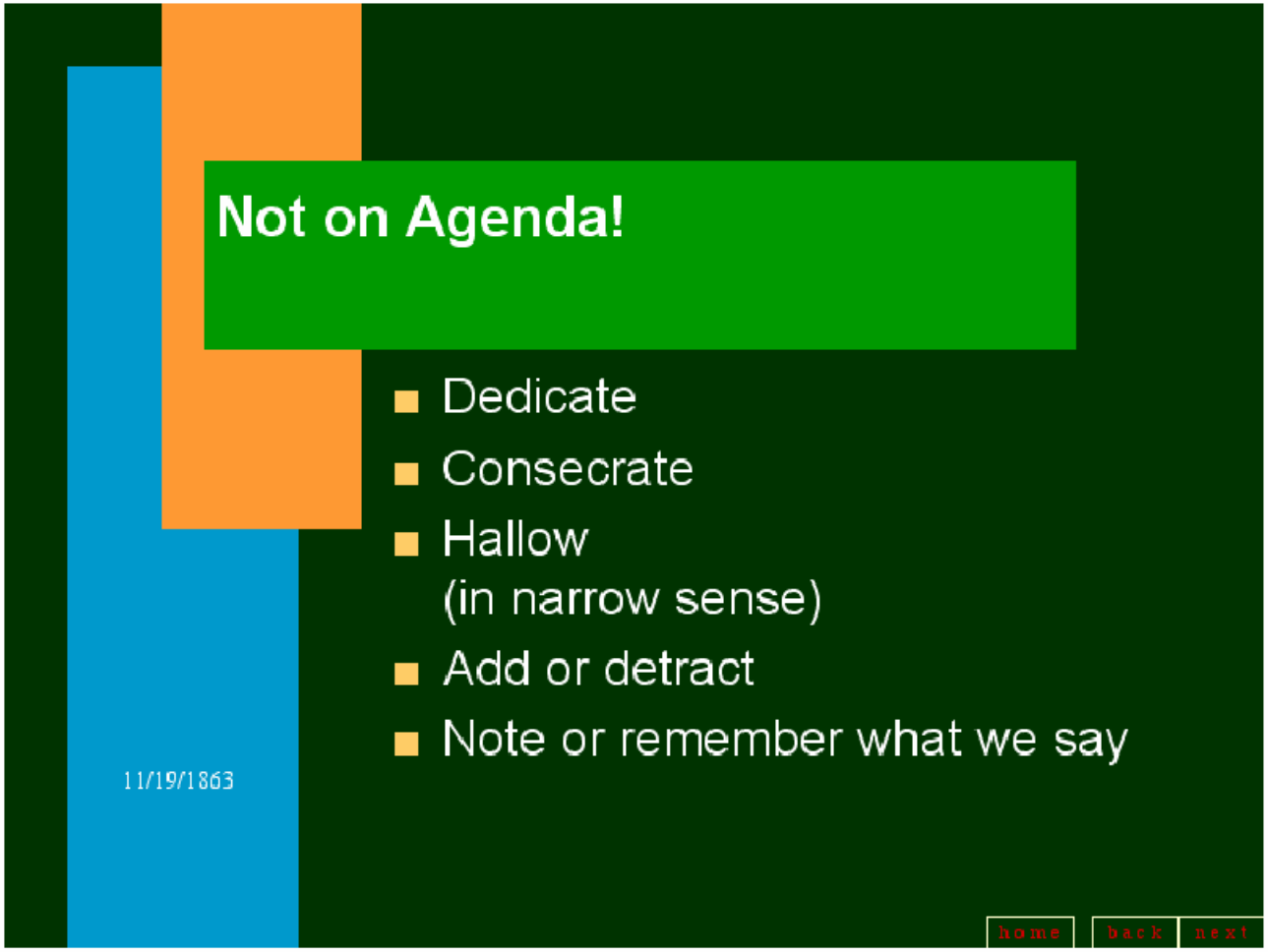
	P-value	# animals
OFA		92
Background	0.246	
Cross	0.011	
Background:Cross	**0.003**	
OFD		92
Background	0.001	
Cross	0.115	
Background:Cross	**0.022**	

DBA

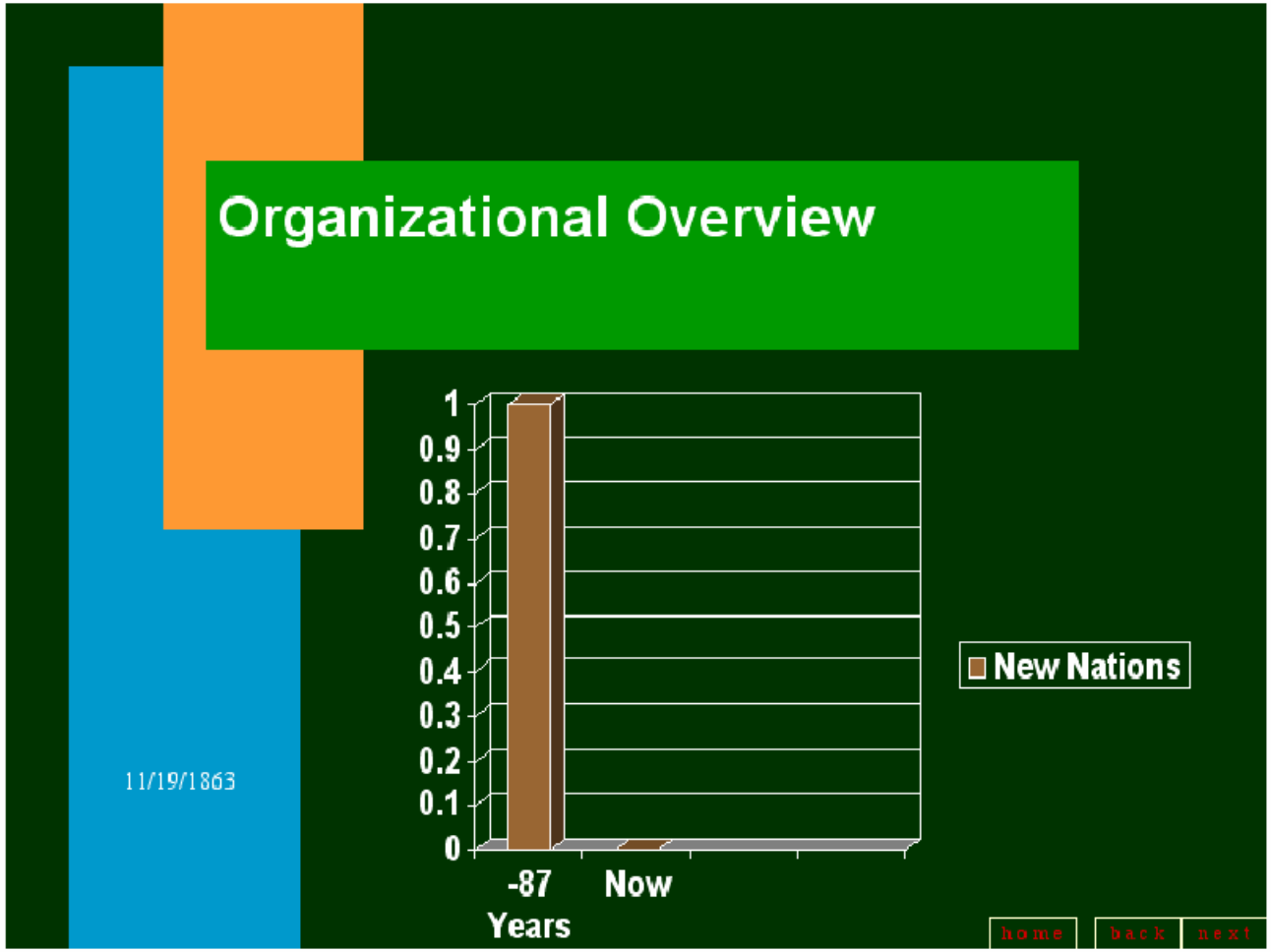
	P-value	# animals
OFA		92
Background	0.008	
Cross	0.083	
Background:Cross	**0.556**	
OFD		92
Background	0.057	
Cross	0.000	
Background:Cross	**0.352**	

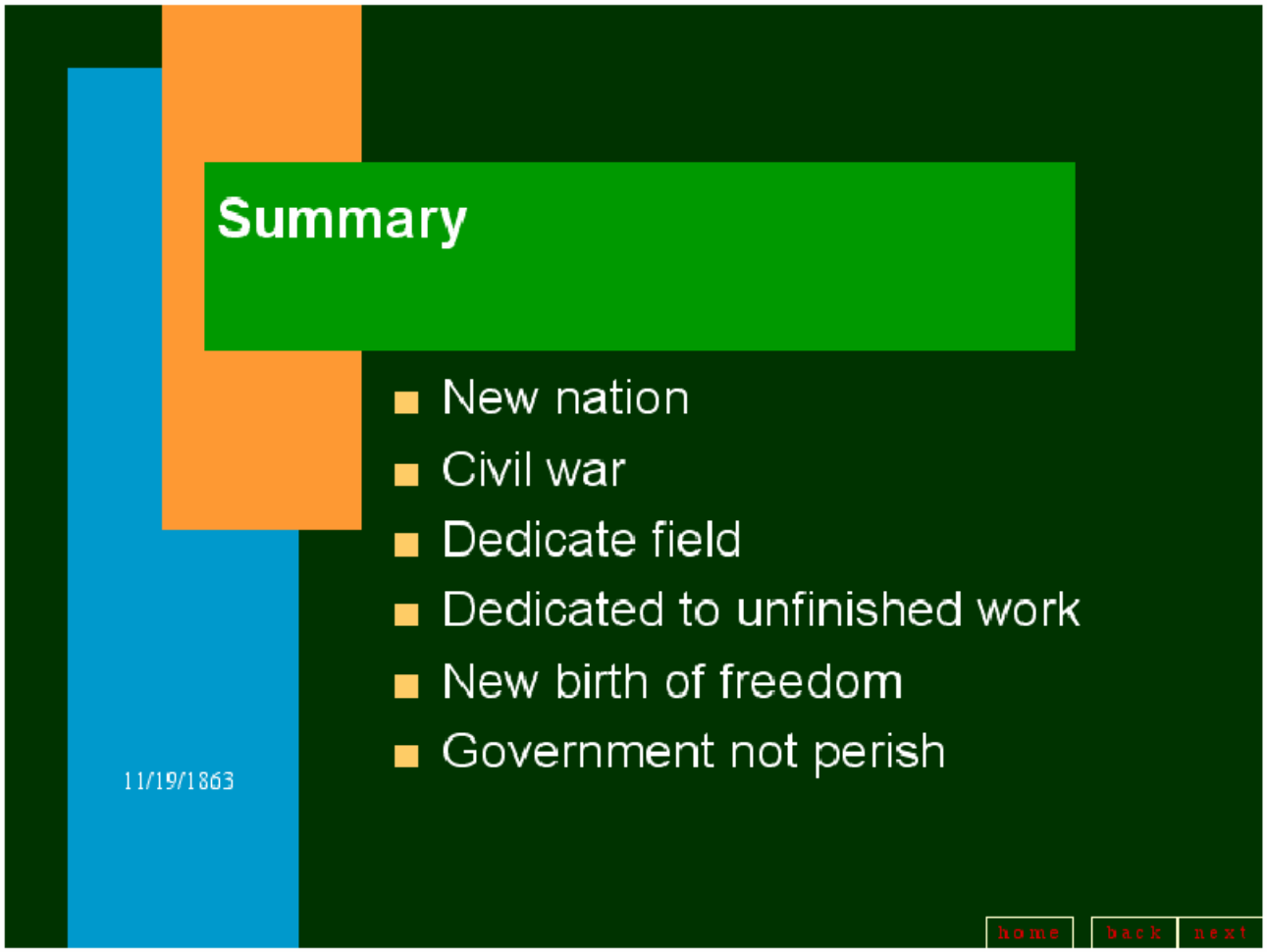

Gettysburg Cemetery Dedication
Abraham Lincoln
11/19/1863
home
back
next


Agenda
Met on battlefield (great)
Dedicate portion of field - fitting!
Unfinished work (great tasks)
11/19/1863
home
back
next


Not on Agenda!
Dedicate
Consecrate
Hallow
(in narrow sense)
Add or detract
Note or remember what we say
11/19/1863
home
back
next


Review of Key Objectives
& Critical Success Factors
What makes nation unique
Conceived in Liberty
Men are equal
Shared vision
New birth of freedom
Gov't of/for/by the people
11/19/1863
home
back
next


Organizational Overview
11/19/1863
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-87
Now
Years
New Nations
home
back
next


Summary
New nation
Civil war
Dedicate field
Dedicated to unfinished work
New birth of freedom
Government not perish
11/19/1863
home
back
next