

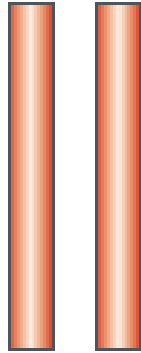
Genetic basis of behavioural differences in rodents

Jonathan Flint

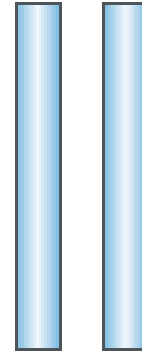
Wellcome Trust Centre for Human Genetics, Oxford
University

Inbred Strain Cross

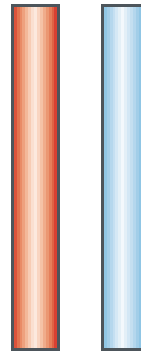
Inbred strain A



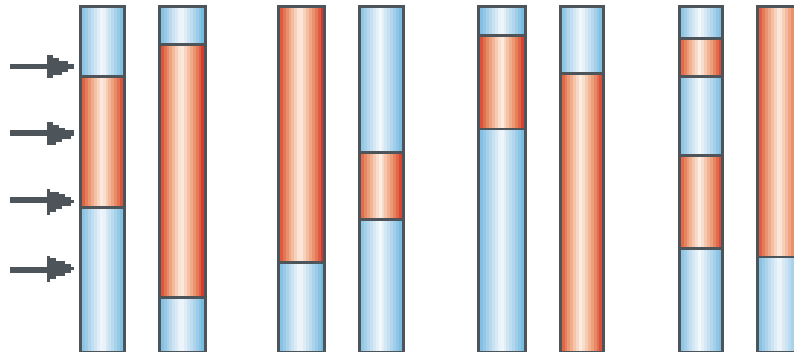
Inbred strain B



F₁

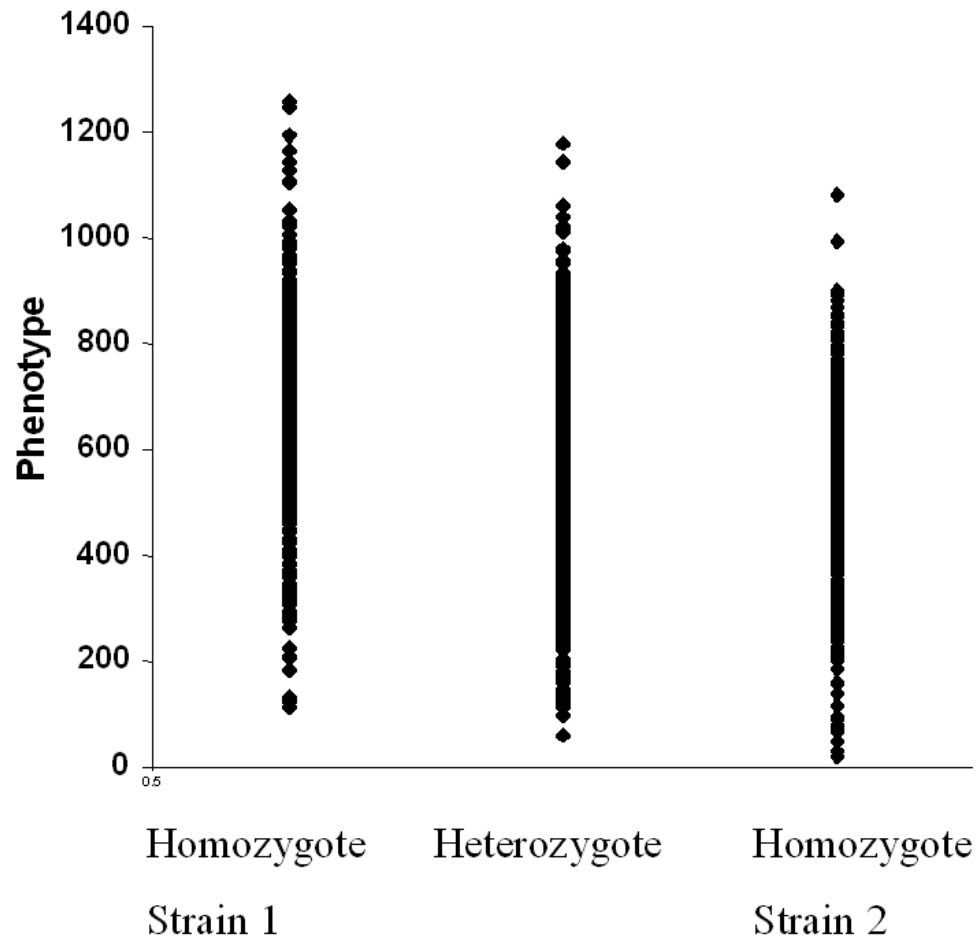


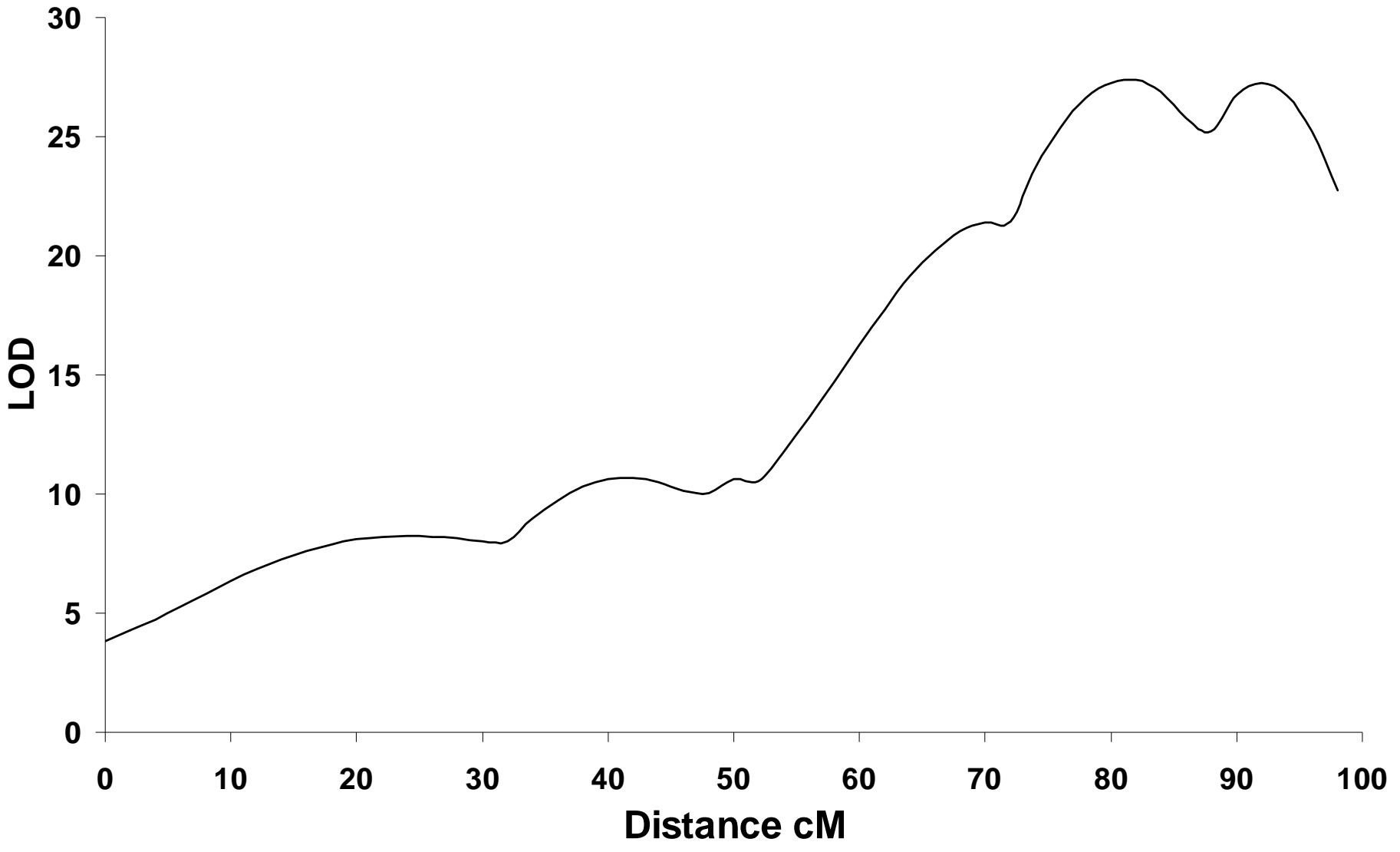
Markers
~30 cM
apart

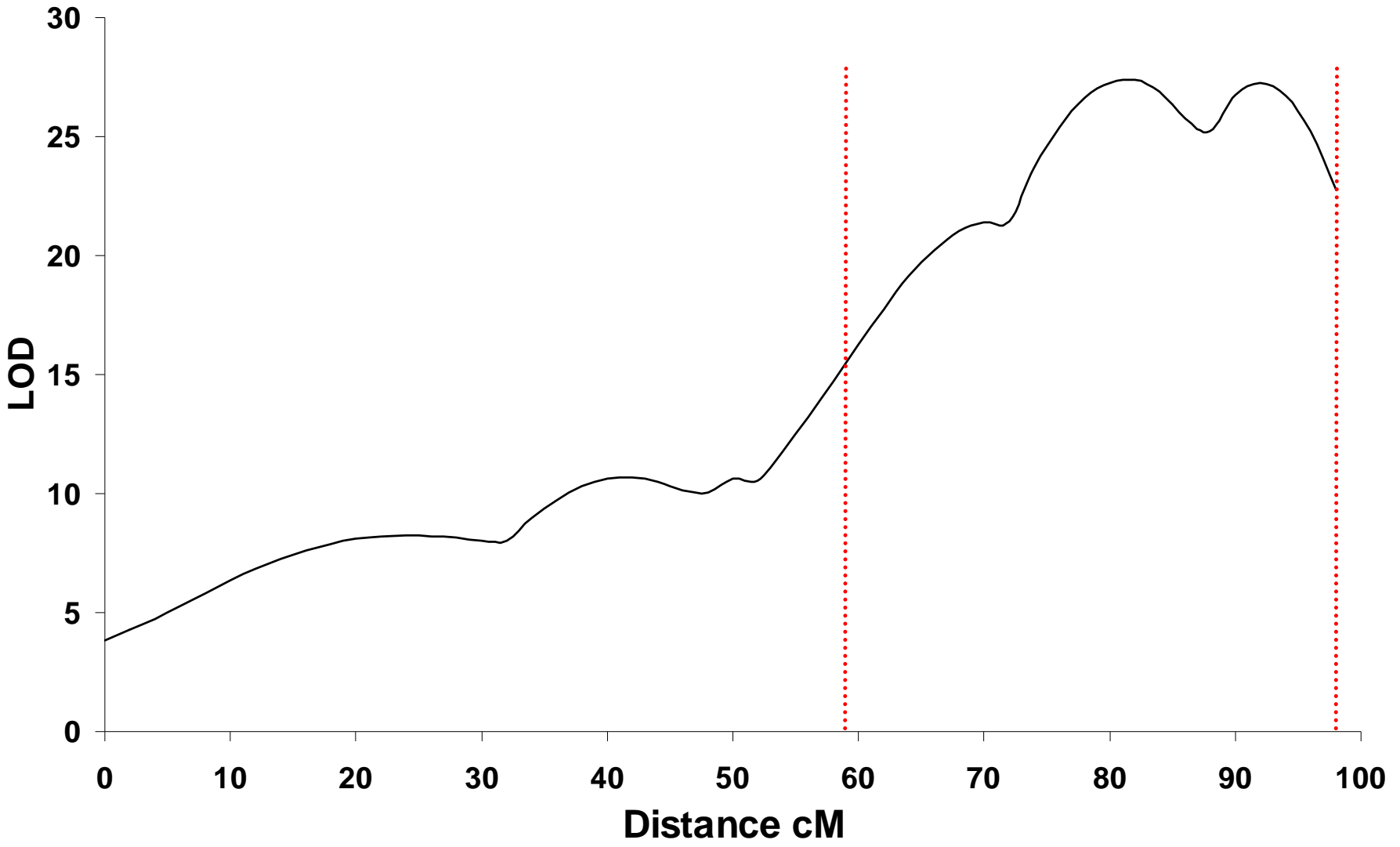


F₂

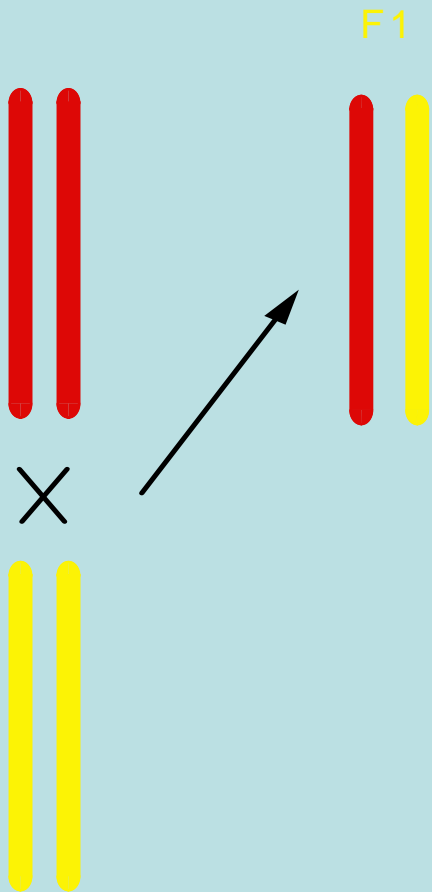
QTL Mapping



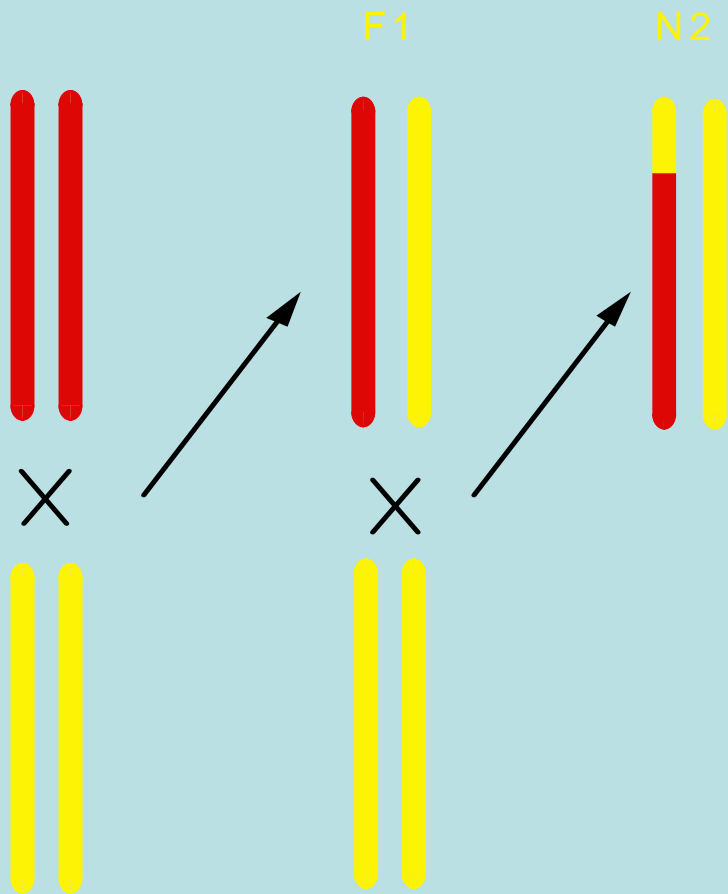




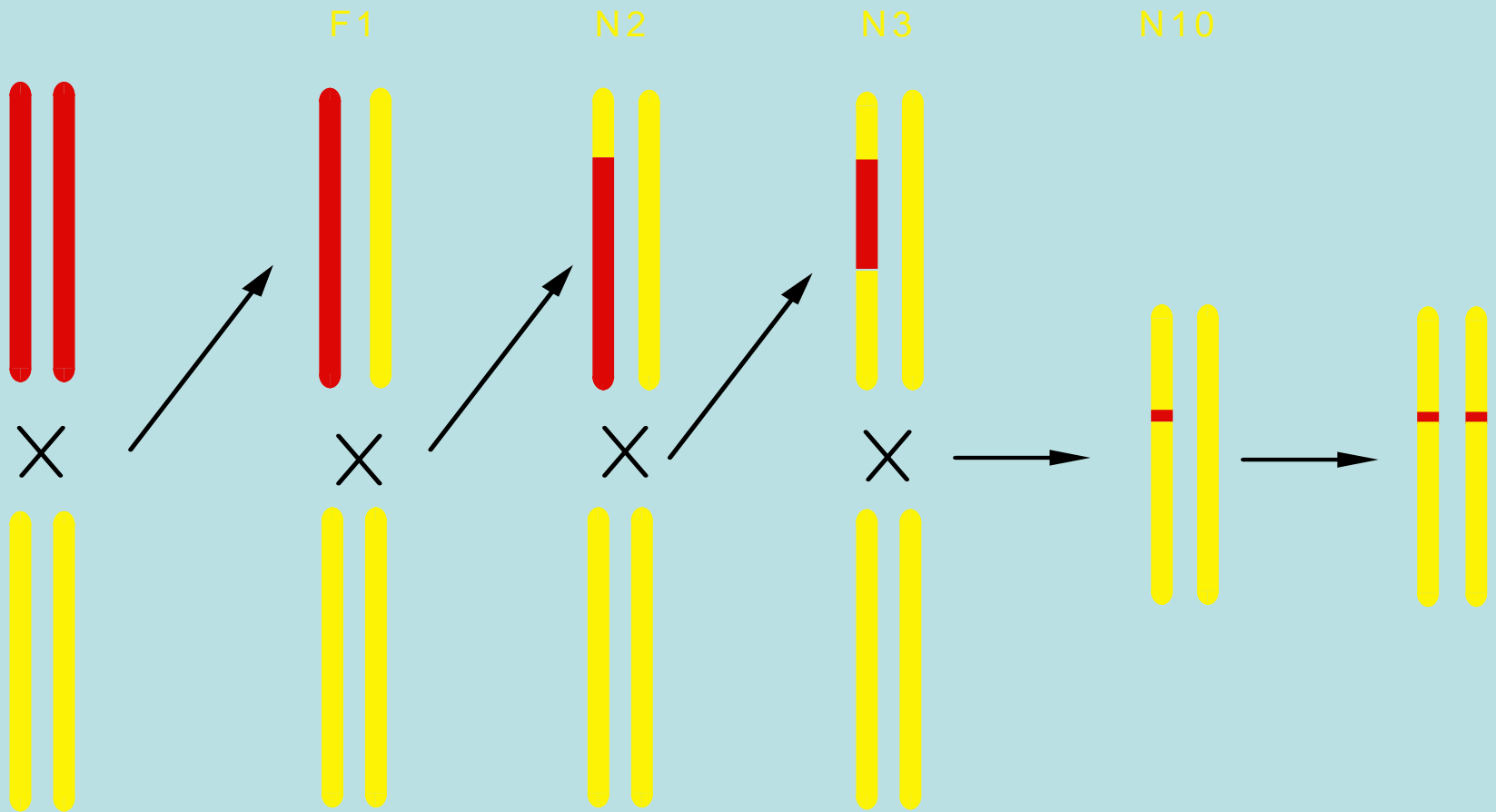
Congenetic Strategy



Congenic Strategy



Congenic Strategy



Why hasn't it worked?

Why hasn't it worked?

- Small effect size

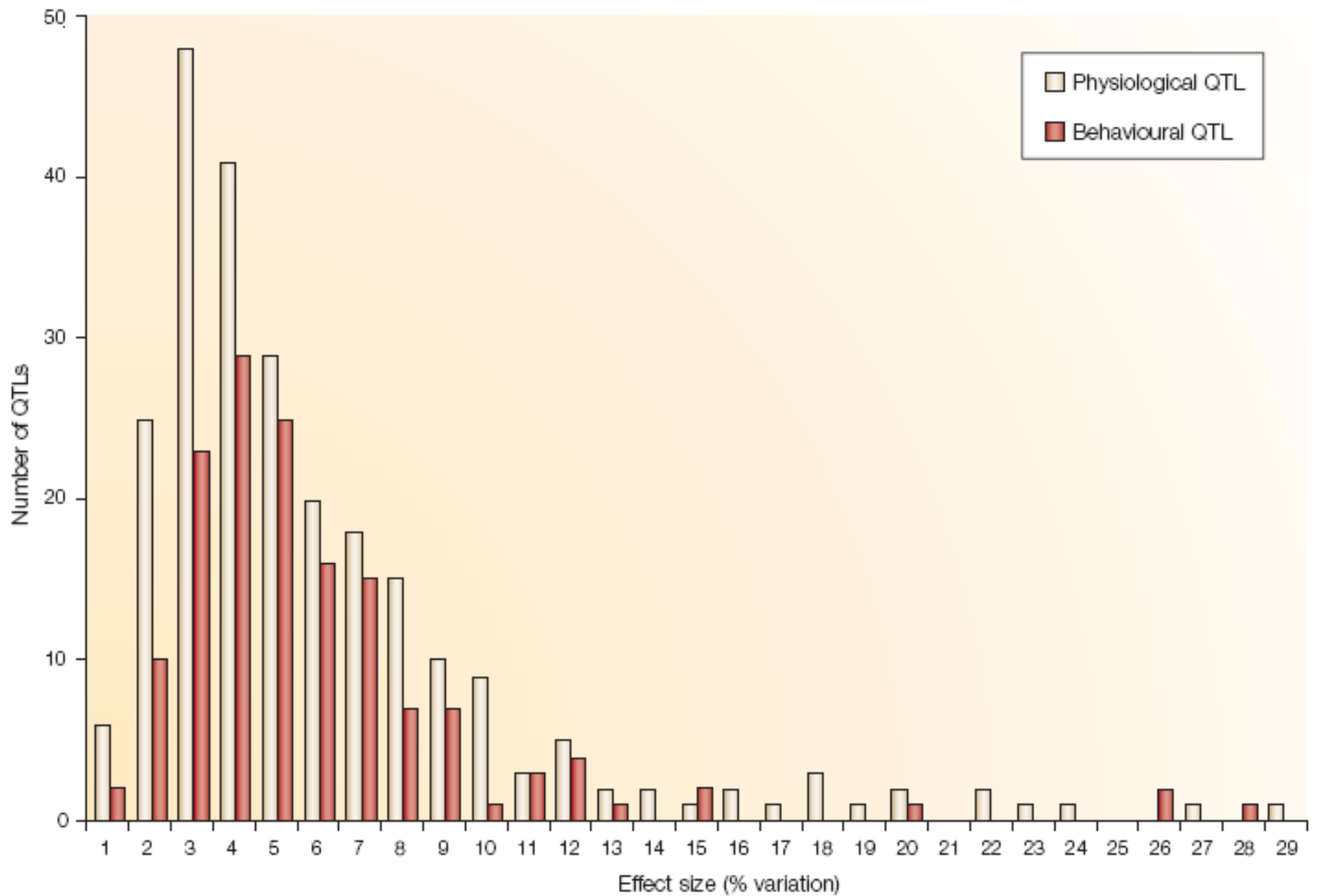


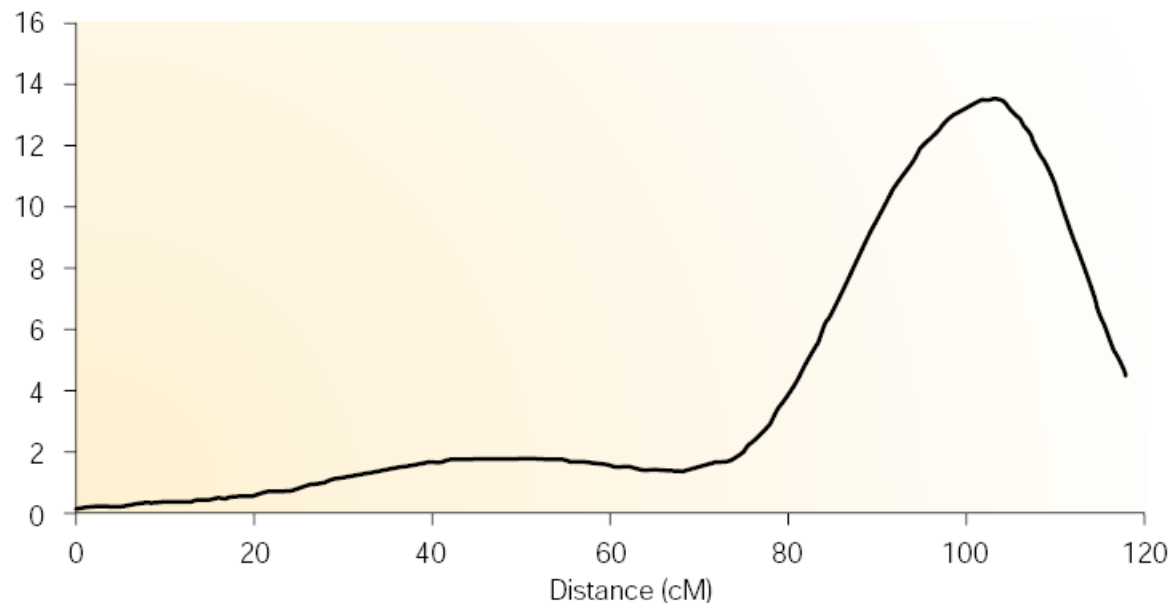
Figure 1 | **The distribution of QTL effect sizes.** Data are from 14 recent quantitative trait loci (QTL) mapping experiments (including 244 significant QTLs). Behavioural QTL data are from REF. 116. Data for physiological QTLs are from REFS 140–153.

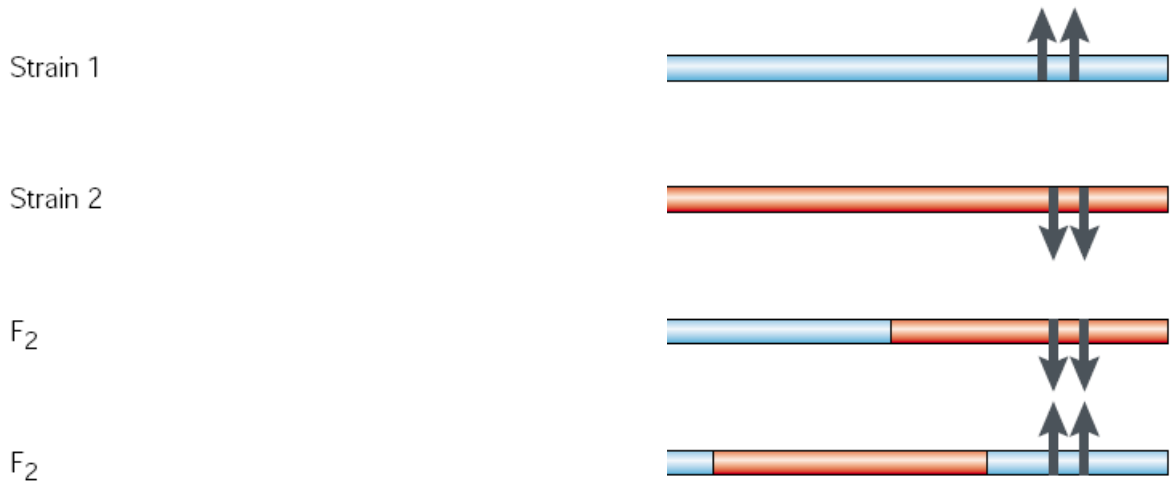
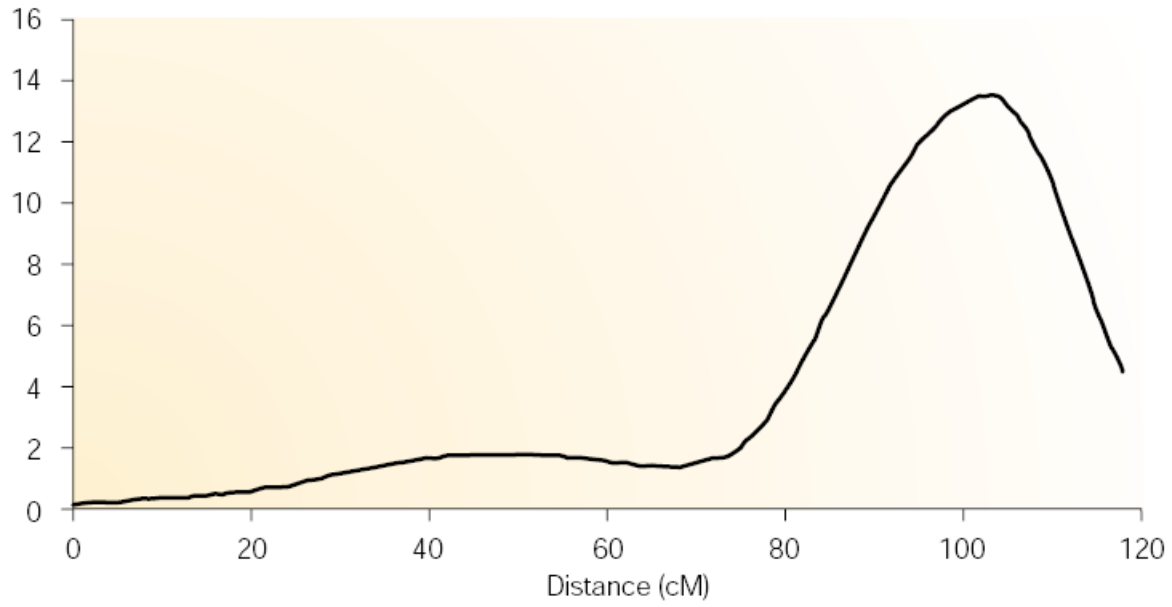
Why hasn't it worked?

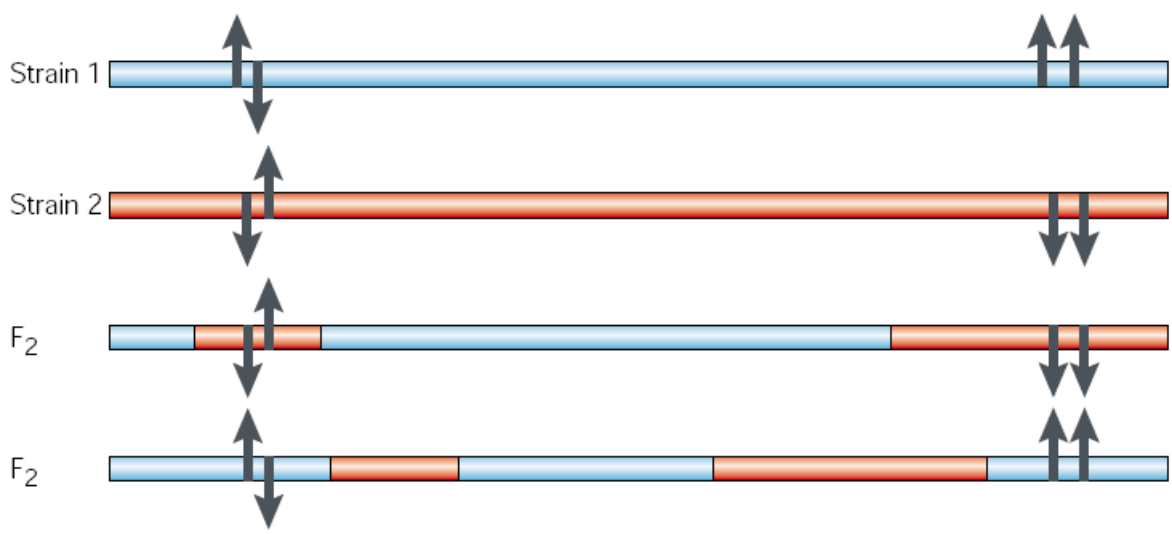
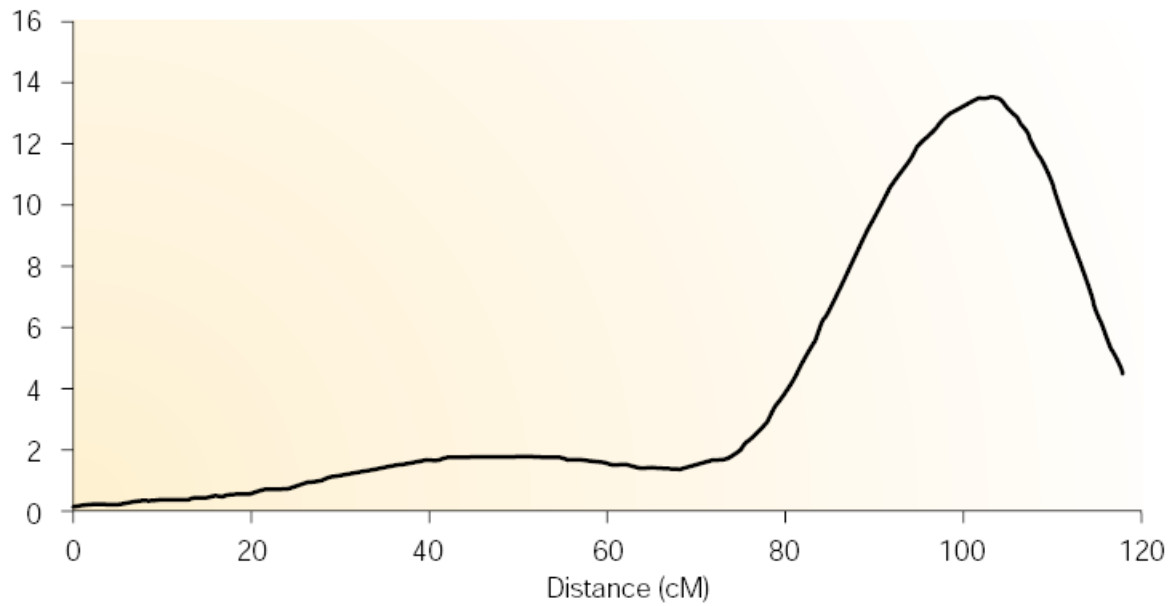
- Small effect size
- No recognizable molecular signature

Why hasn't it worked?

- Small effect size
- No recognizable molecular signature
- Multiple linked genetic effects







Approaches

Approaches

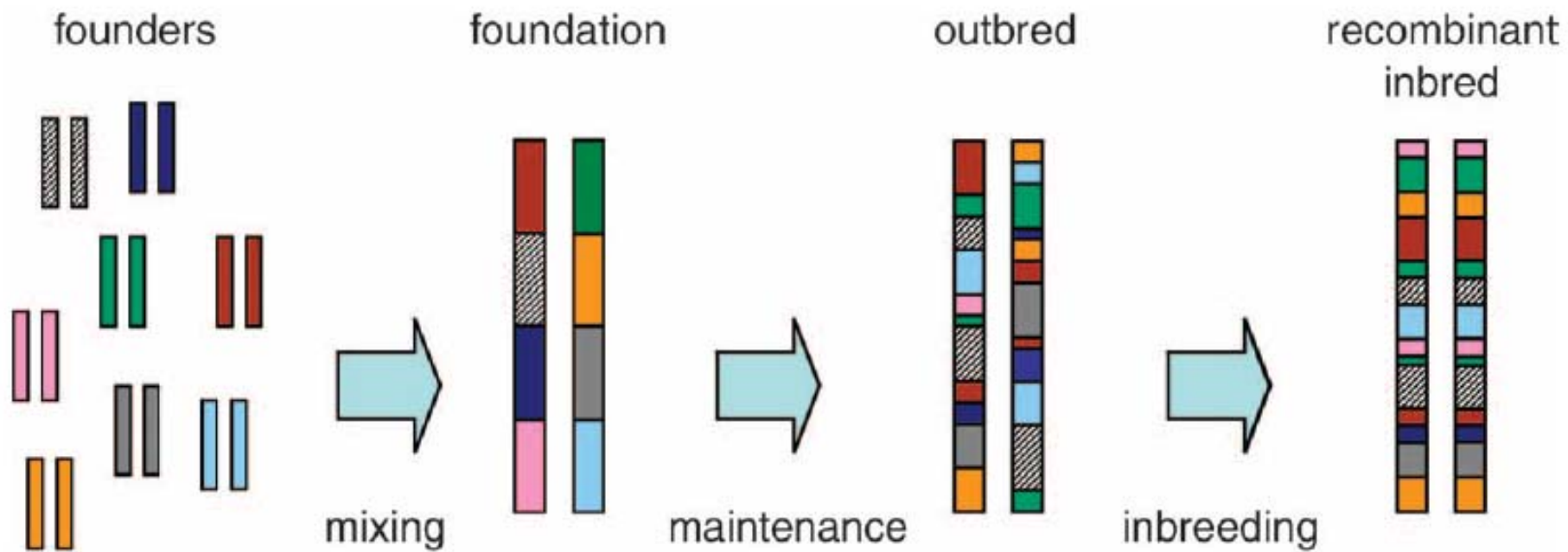
- Collaborative cross
- In silico mapping
- Outbreds
- ENU/Knock outs

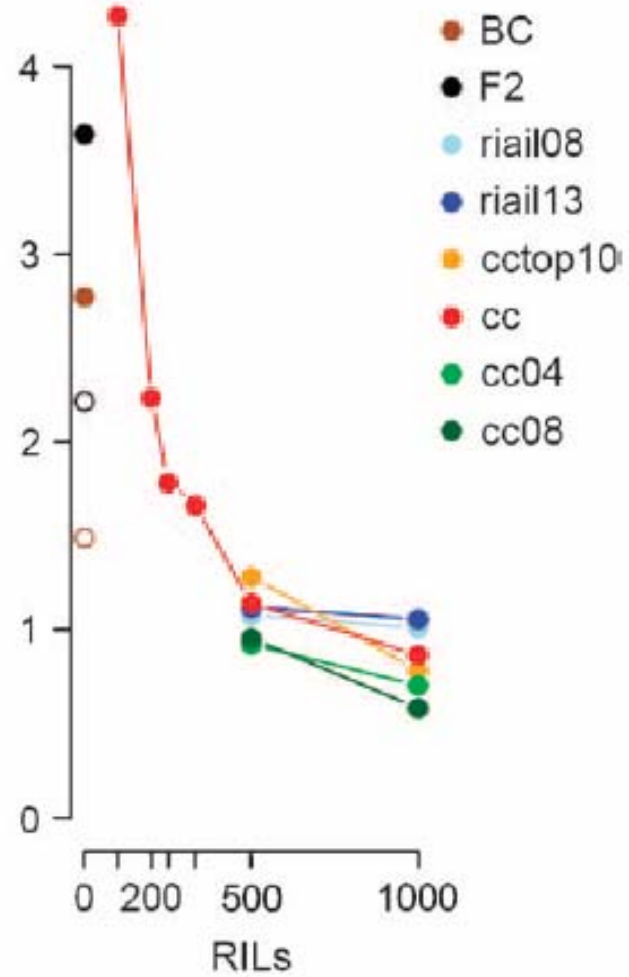
Collaborative Cross

The Collaborative Cross, a community resource for the genetic analysis of complex traits

The Complex Trait Consortium*

NATURE GENETICS VOLUME 36 | NUMBER 11 | NOVEMBER 2004





Genetics 172: 1783–1797 (March 2006)

In silico mapping

In Silico Mapping of Complex Disease-Related Traits in Mice

**Andrew Grupe,^{1*} Soren Germer,^{2*} Jonathan Usuka,^{3*} Dee Aud,¹
John K. Belknap,⁴ Robert F. Klein,⁴ Mandeep K. Ahluwalia,²
Russell Higuchi,² Gary Peltz^{1†}**

www.sciencemag.org SCIENCE VOL 292 8 JUNE 2001

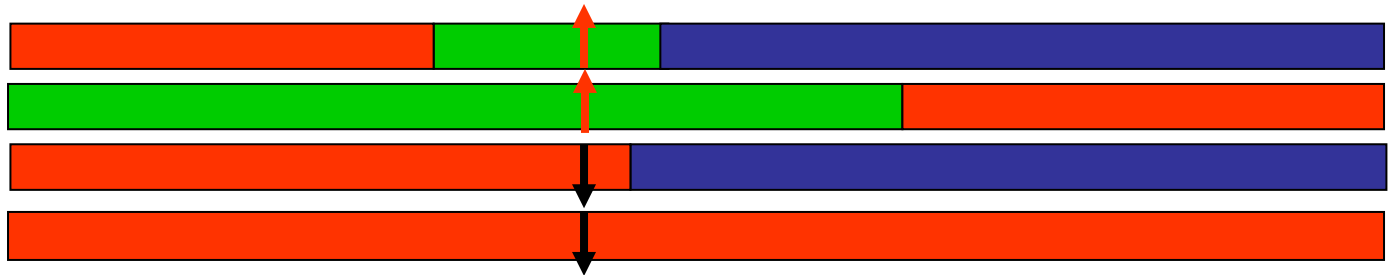
Candidate lung tumor susceptibility genes identified through whole-genome association analyses in inbred mice

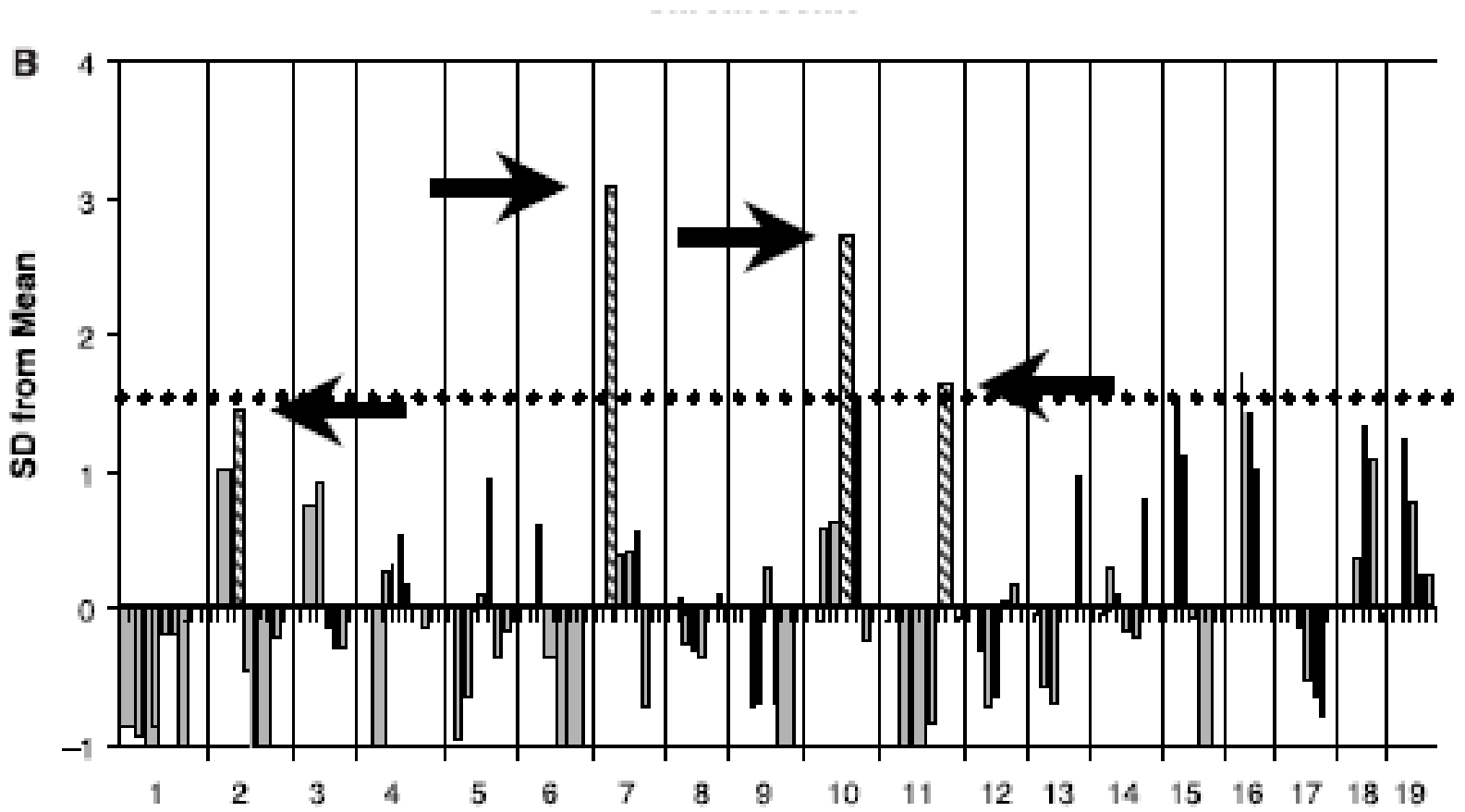
Pengyuan Liu^{1,2}, Yian Wang^{1,2}, Haris Vikis^{1,2}, Anna Maciag^{1,2}, Daolong Wang¹, Yan Lu¹, Yan Liu¹ & Ming You¹

Sequence differences among
inbred strains must be consistent
with genetic action

Sequence differences among inbred strains must be consistent with genetic action

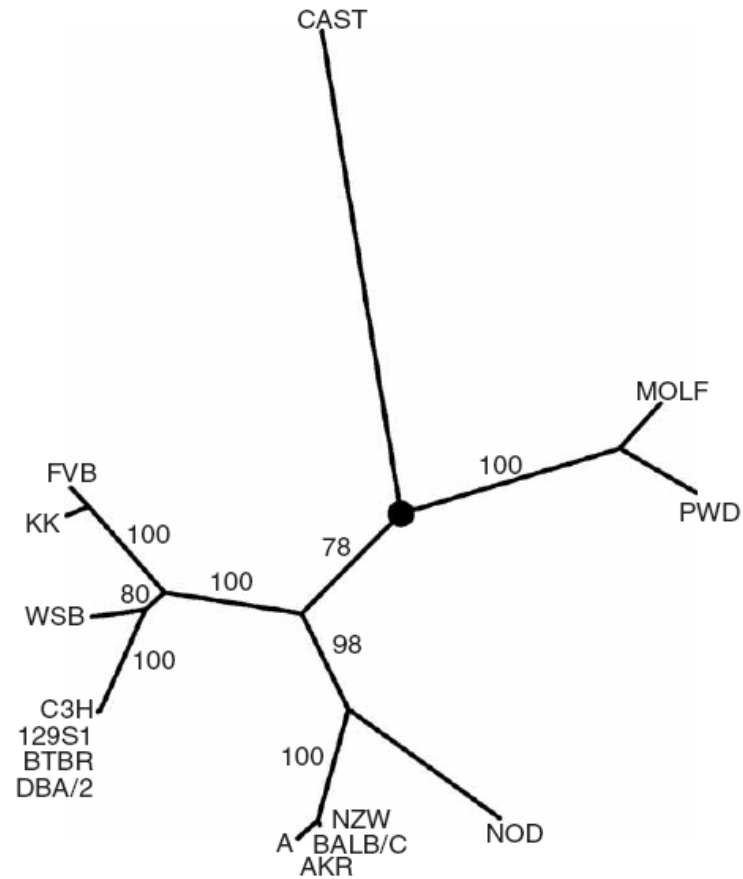
Genetic effect (or QTL)





In silico mapping

- Genetic relatedness of strains



On the subspecific origin of the laboratory mouse

Hyuna Yang¹, Timothy A Bell², Gary A Churchill¹ & Fernando Pardo-Manuel de Villena²

Model	Median logP
No genetic component	4.1

SNP and haplotype mapping for genetic analysis in the rat

The STAR Consortium*

Model	Median logP
No genetic component	4.1
Infinitesimal model accounts for 50% of variance	21.5
Ten 5% QTLs	9.96

SNP and haplotype mapping for genetic analysis in the rat

The STAR Consortium*

Supplementary Table 2: In silico mapping. Median number of putative QTL exceeding given LogP threshold for a scenario of ten 5% QTL. One hundred inbred Rat strains were evaluated by simulation for their potential for WGA mapping of QTL.

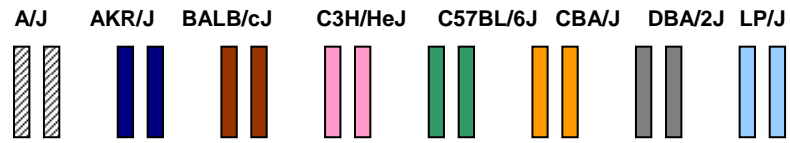
LogP threshold	# putative QTL
4.1	1,412.0
5	681.5
6	248.0
7	154.0
8	19.5

SNP and haplotype mapping for genetic analysis in the rat

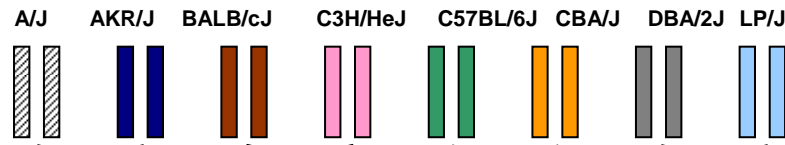
The STAR Consortium*

Outbreds

Heterogeneous stocks

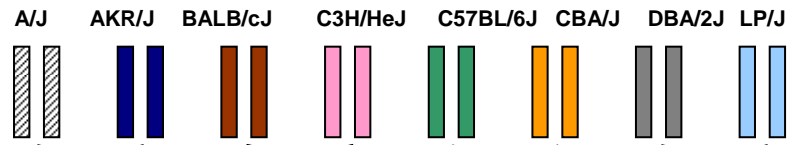


Heterogeneous stocks



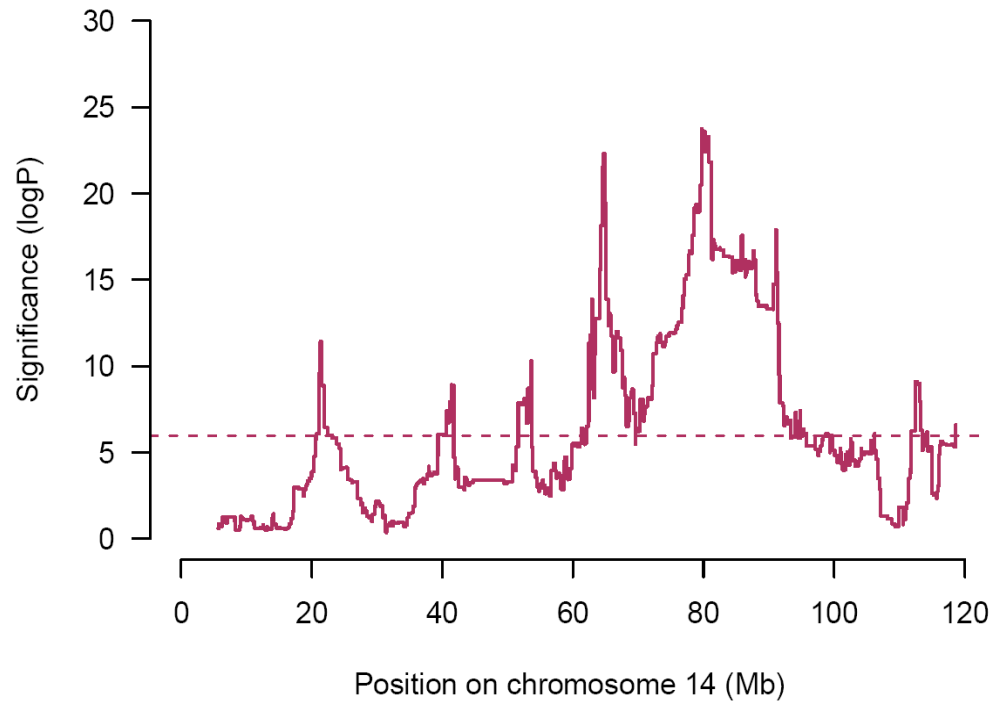
Pseudo-random mating
for 50 generations

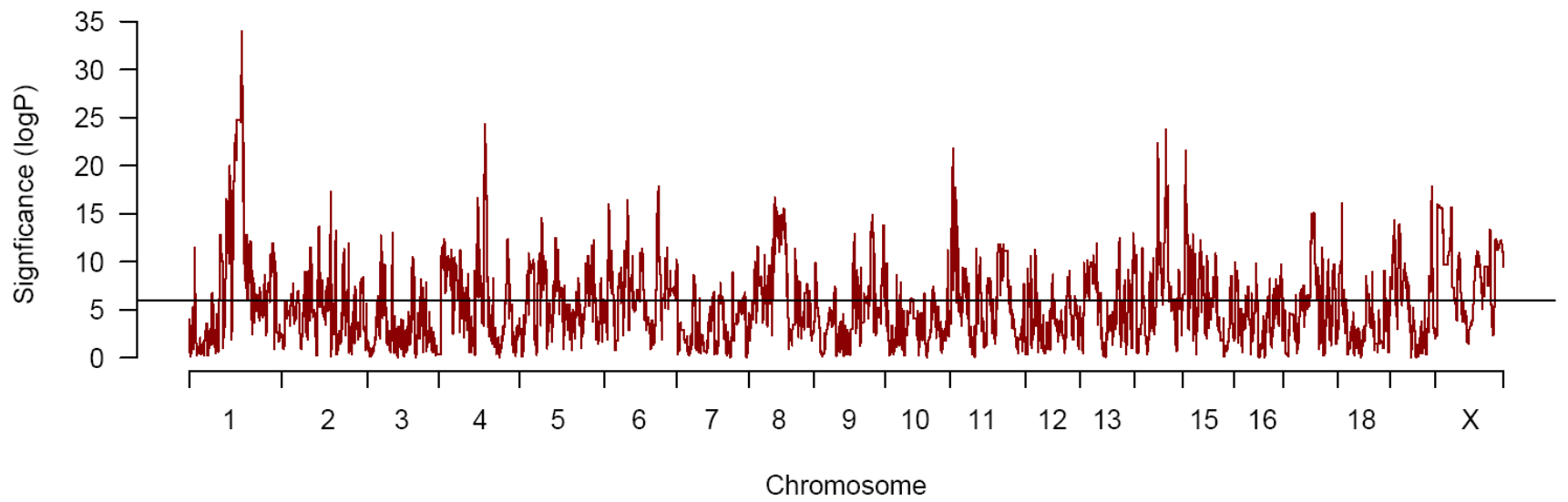
Heterogeneous stocks



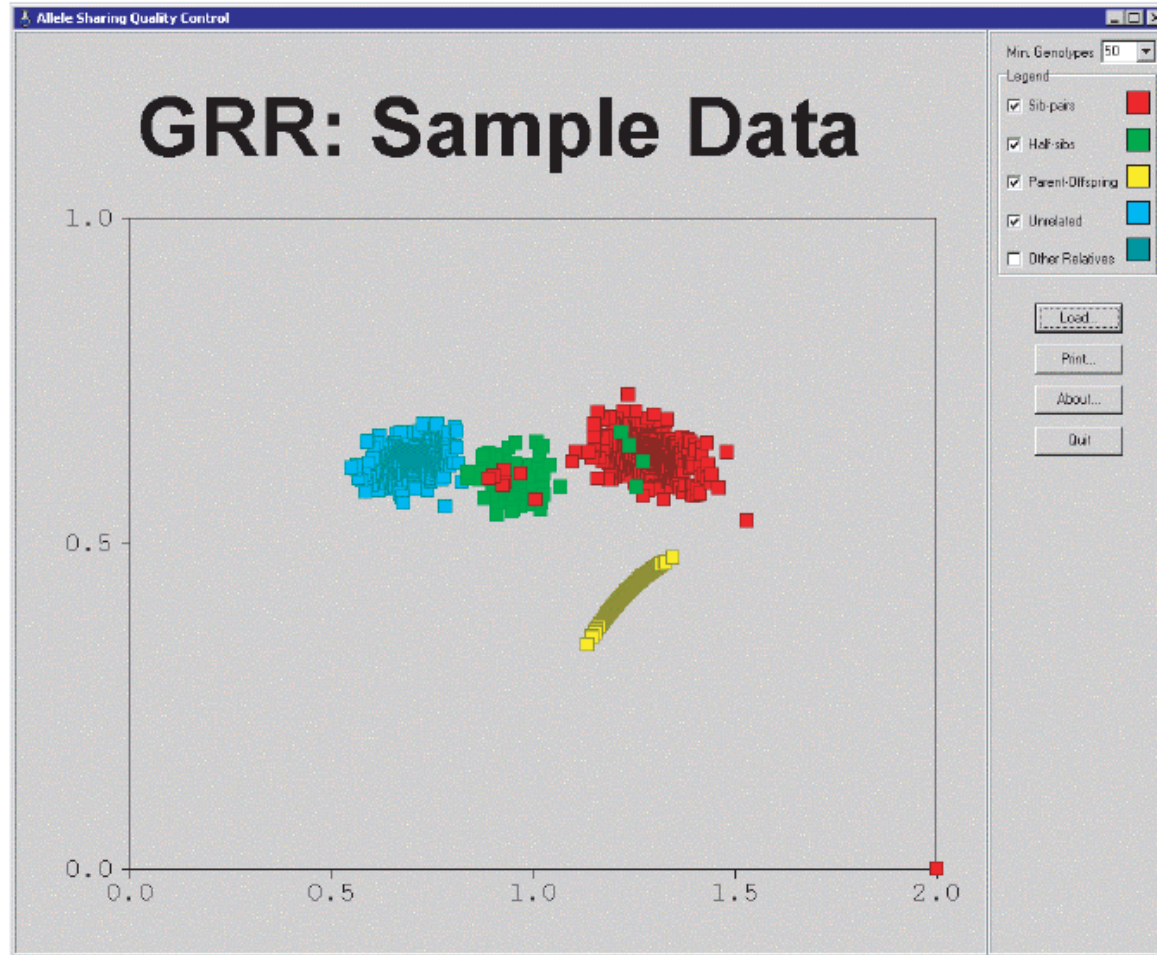
Pseudo-random mating
for 50 generations





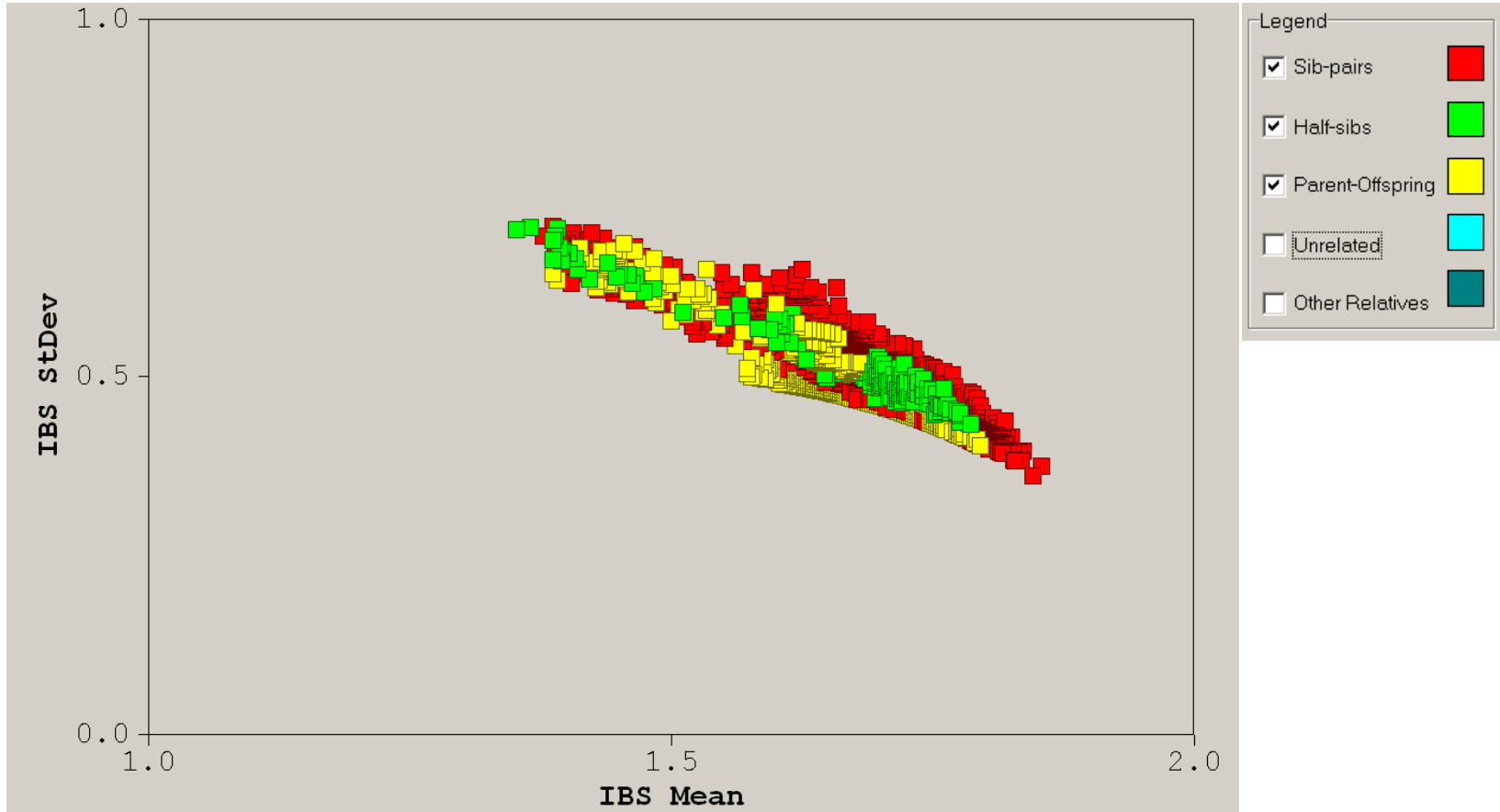


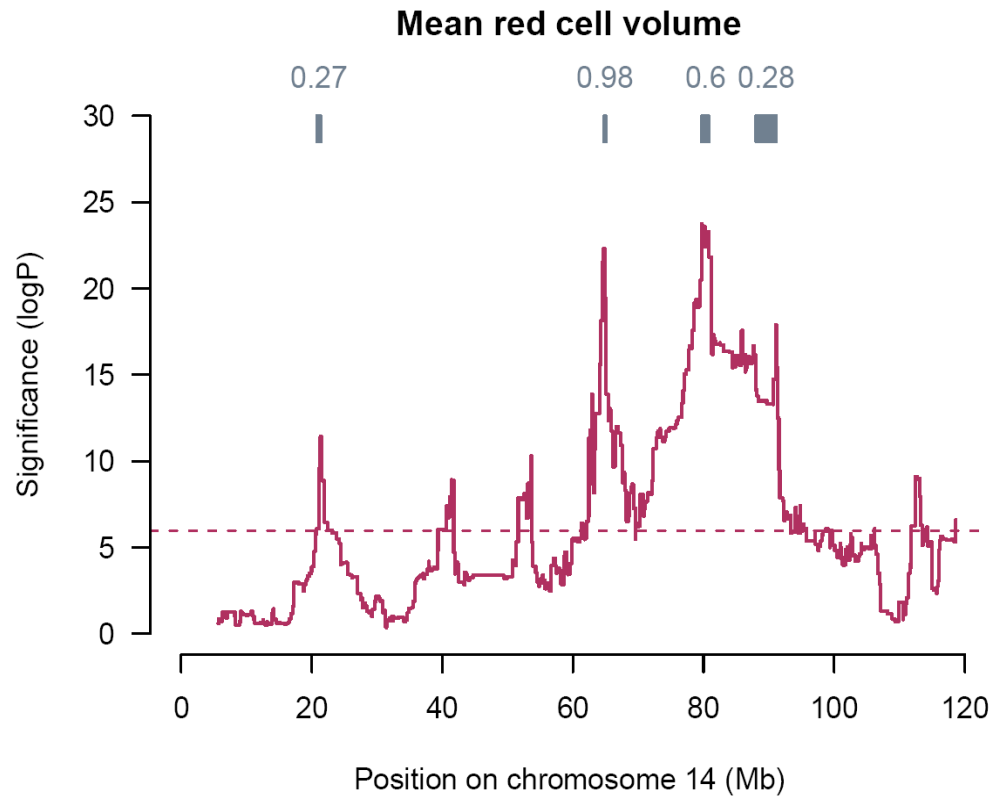
Degree of relatedness: human population



Bioinformatics 17:742-743, 2001, Abecasis et al

Degree of relatedness: HS population





<http://gscan.well.ox.ac.uk/>

$P = 0.00000016$

Negative Log P = 6.4

LOD = 4.4

~~P = 0.00000016~~

~~Negative Log P = 6.4~~

~~LOD = 4.4~~

<http://gscan.well.ox.ac.uk>

Genetic architecture

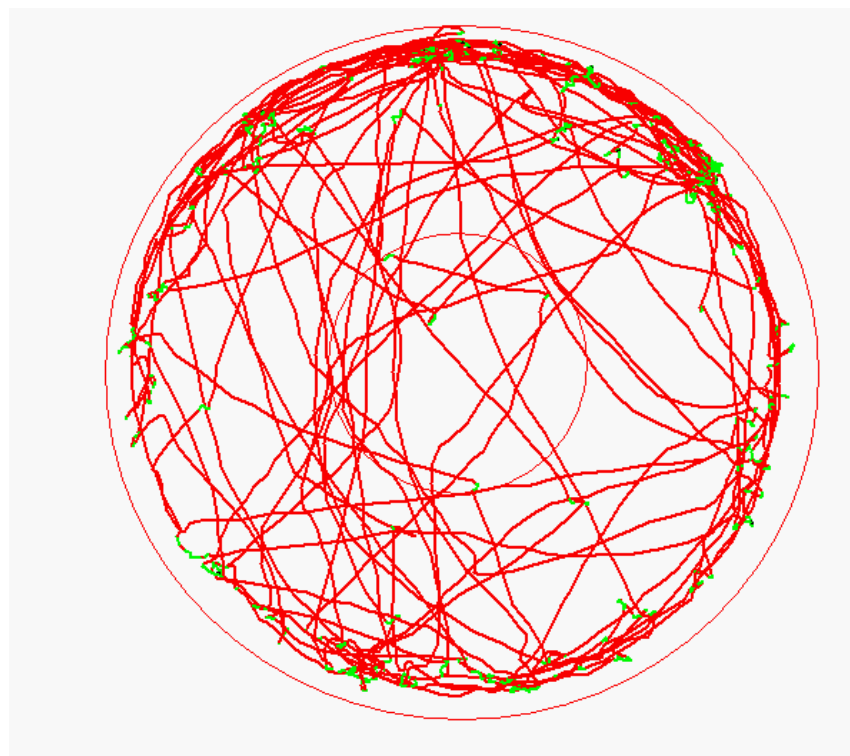
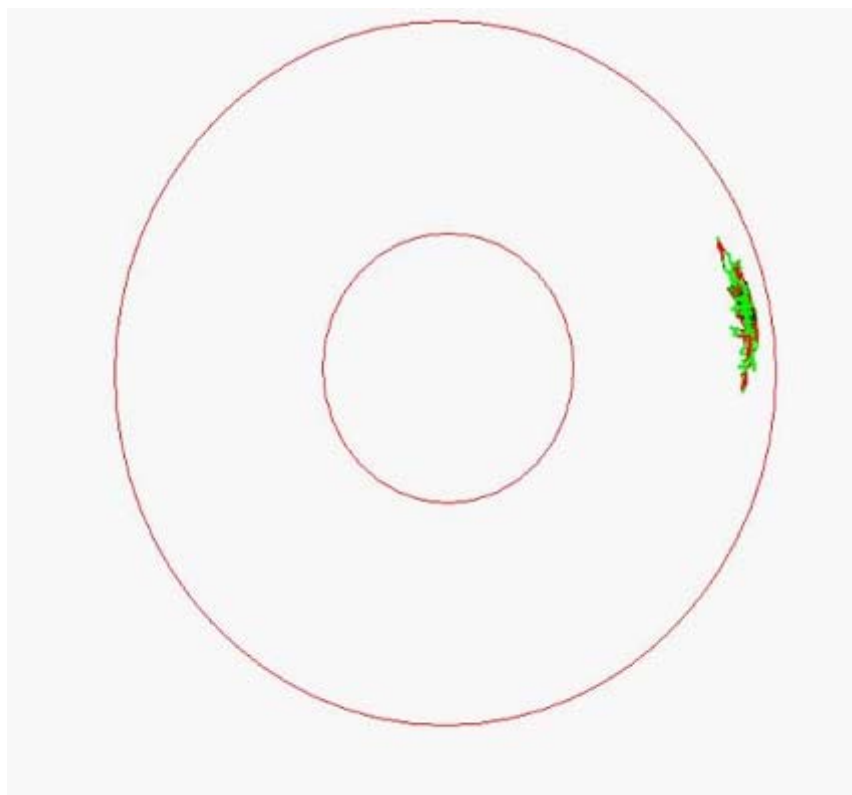
High throughput phenotyping facility





Open Field

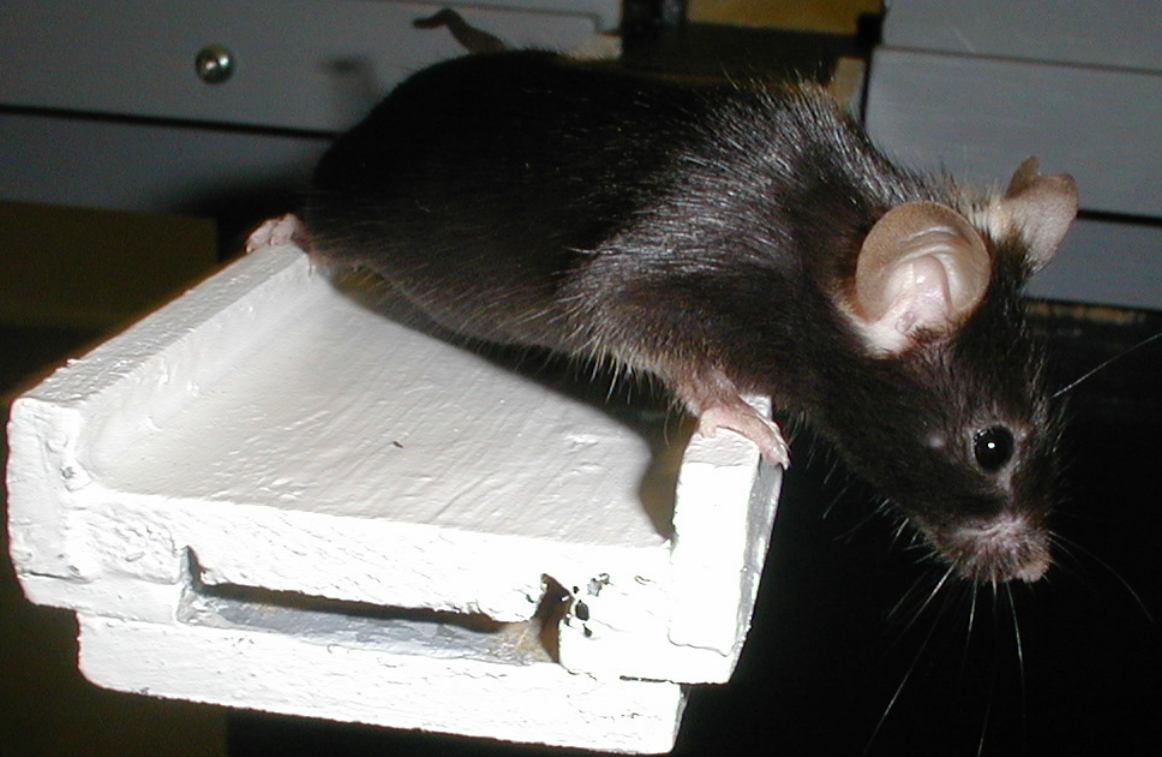
OFA Tracking



Elevated Plus Maze

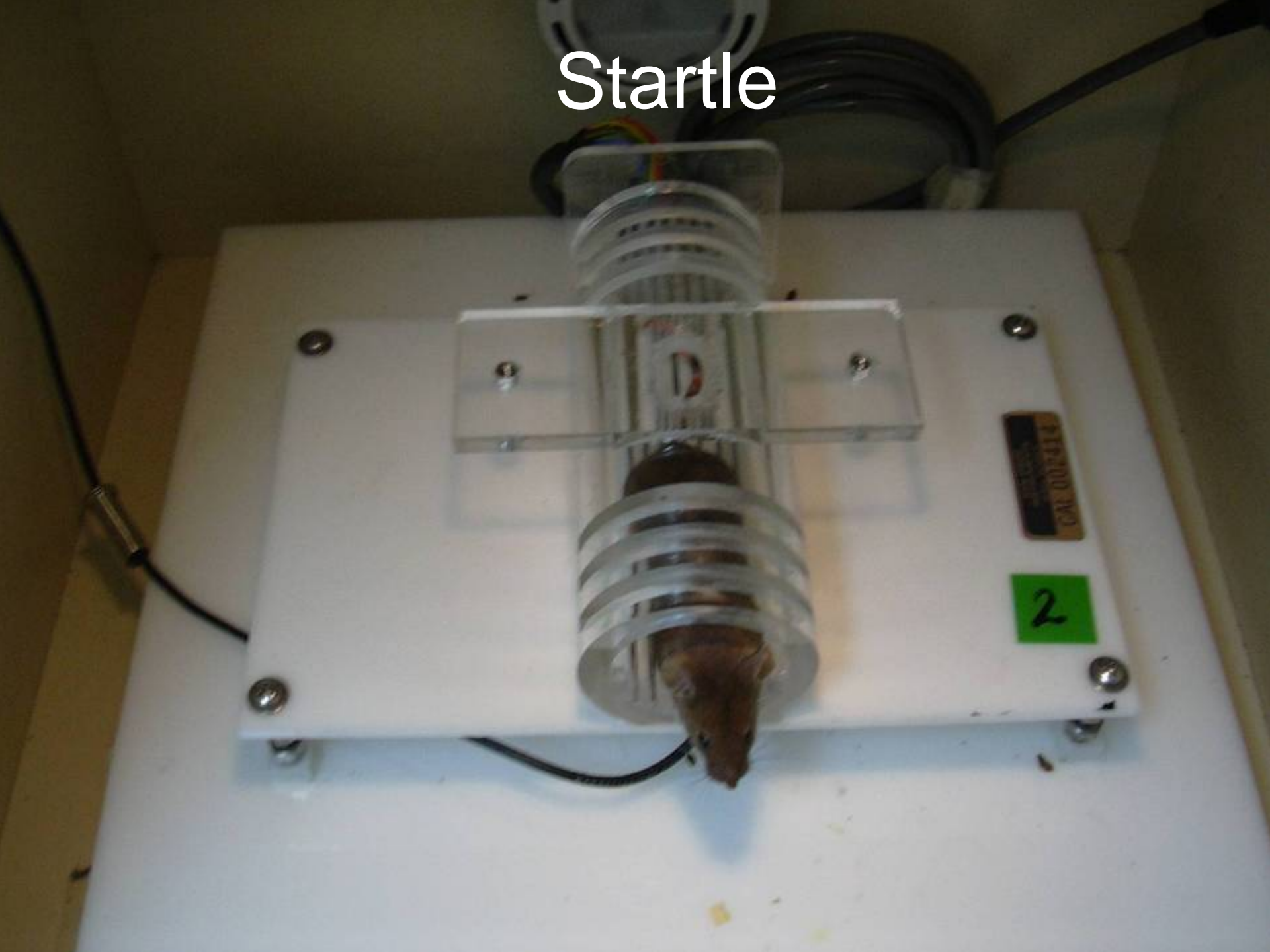








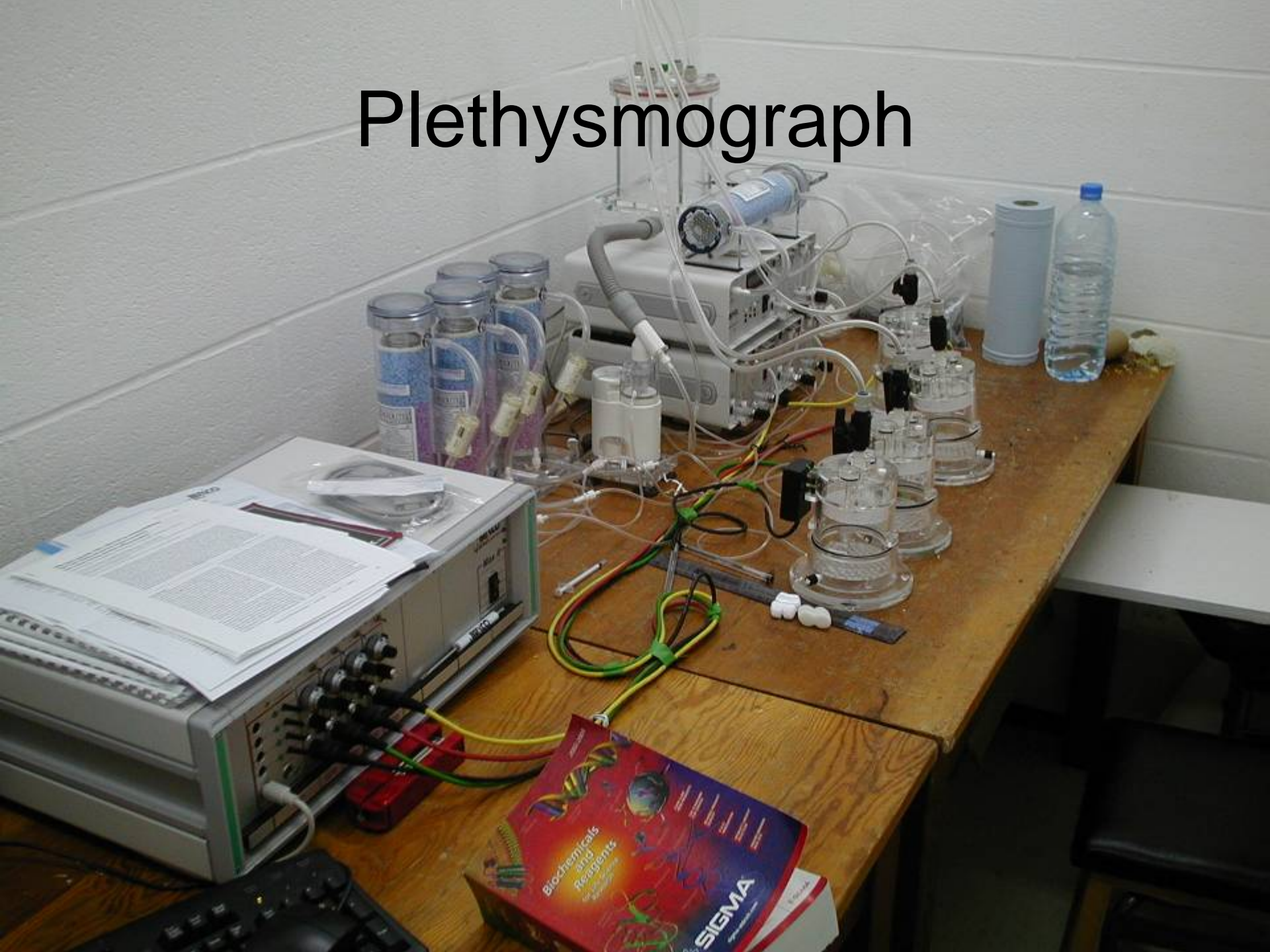
Startle

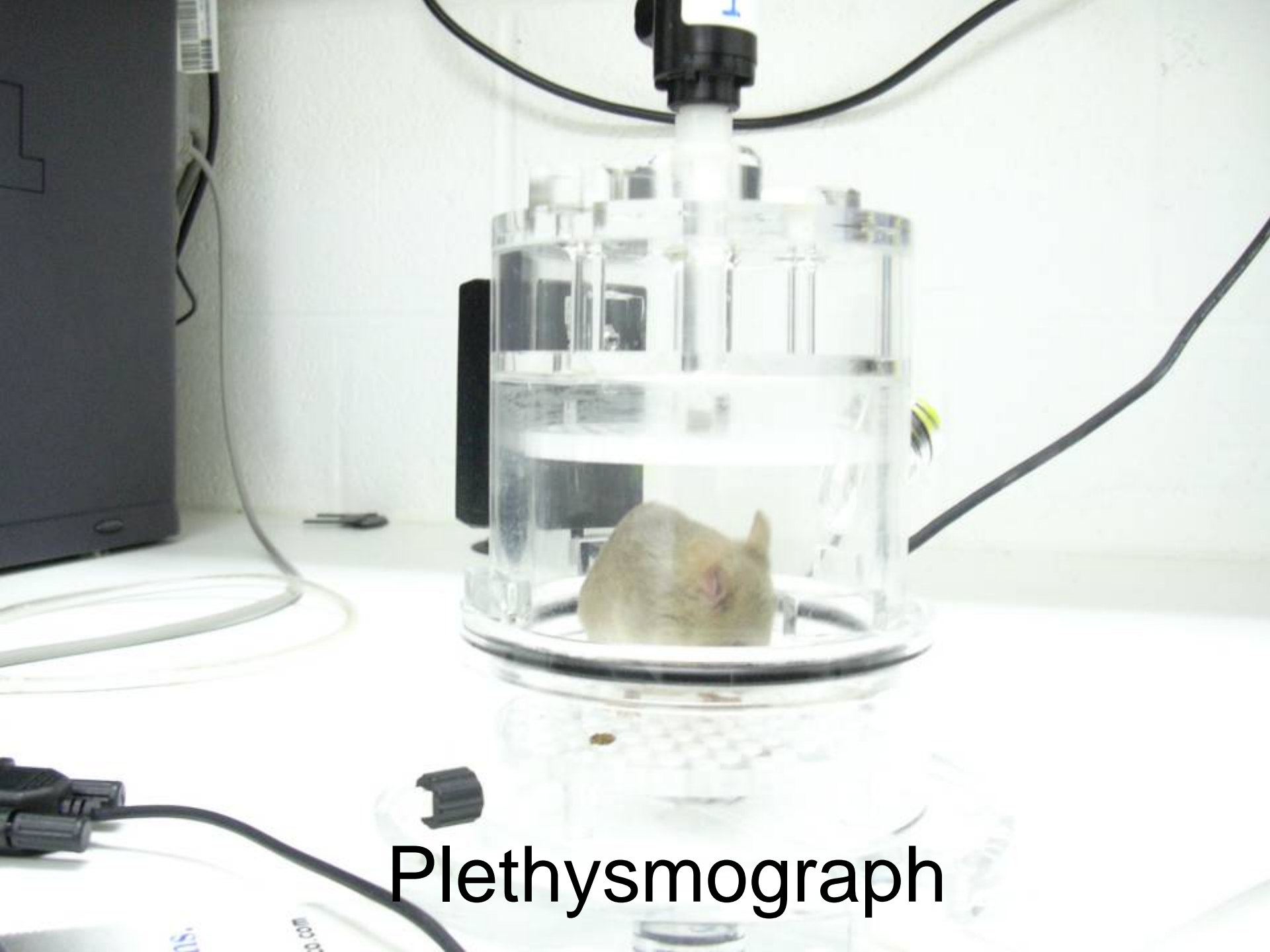




Food hyponeophagia
(reluctance to try new food)

Plethysmograph





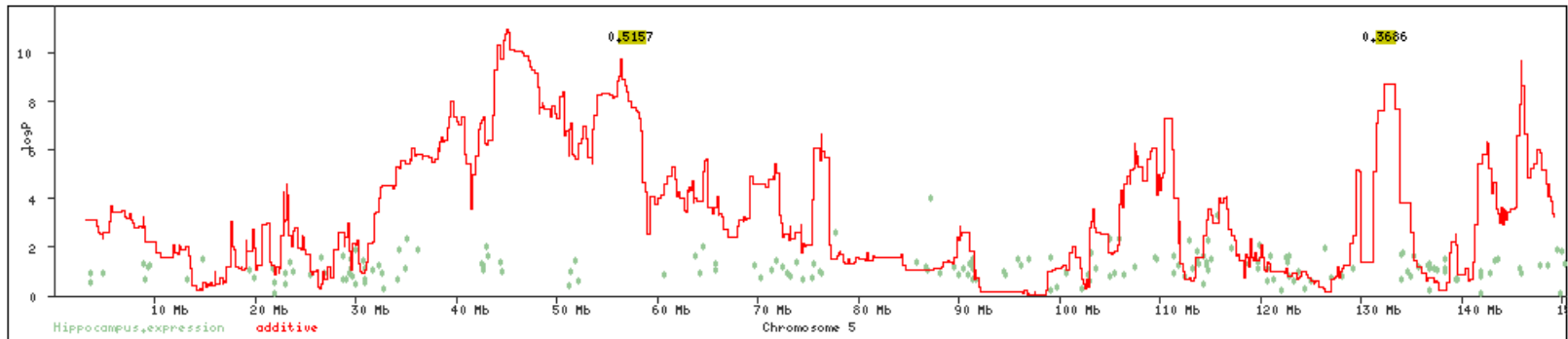
Plethysmograph



Intraperitoneal Glucose Tolerance Test

Test	Measure	Test	Measure	Test	Measure
<i>Open Field Arena</i>	Total Activity	<i>Plethysmography</i>	PenH Difference	<i>Immunology</i>	%B220 ⁺
	Center Time		Respiratory rate (baseline)		%CD3 ⁺
	Latency		Tidal volume (baseline)		%CD4 ⁺
	Faecal Boli		Tidal minute volume (baseline)		%CD8 ⁺
	Activity and defecation		Inspiratory time (baseline)		CD4 ⁺ /CD8 ⁺
<i>Elevated Plus Maze</i>	Closed Arm Distance		Expiratory time (baseline)		%CD4 ⁺ /CD3 ⁺
	Open Arm Distance		Enhanced pause (baseline)		%CD8 ⁺ /CD3 ⁺
	Closed Arm Time		Respiratory rate (metacholine)		%NK cells
	Open Arm Time		Tidal volume (metacholine)		<i>Haematology</i>
	Closed Arm Entries		Tidal minute volume (metacholine)		
	Open Arm Entries	Inspiratory time (metacholine)	Haemoglobin (g/dL)		
	Open Arm Latency	Expiratory time (metacholine)	Mean cellular volume(fL)		
<i>Food Hyponeophagia</i>	FN Latency	Enhanced pause (metacholine)	Platelets (n/uL)		
<i>New home-cage activity</i>	Total beam breaks (30 minutes)	<i>IPGTT</i>	AUC-G (mg/dL)	Red blood cell count (n/uL)	
	Total beam breaks (First five minutes)		DG (mg/dL)	White blood cell count (n/uL)	
	Total beam breaks (Last five minutes)		Glucose 0 (mg/dL)	Basophils	
	Fine Movement		Glucose 15 (mg/dL)	Monocytes	
			Glucose 30 (mg/dL)	Mean platelet volume (fL)	
<i>Species-typical behaviour</i>	Pellets Burrowed		Glucose 75 (mg/dL)	Neutrophils	Mean cellular Hb conc. (%)
			K (glucose slope)	Red cell distribution width	
<i>Context Freezing</i>	Minutes freezing		AUC-IRI (ng/ml)	Mean corpuscular haemoglobin (pg)	
			DIRI (ng/ml)	Lymphocytes	
<i>Cue Conditioning</i>	Minutes freezing during cue		Insulin Slope	Plateletcrit (%)	
	Minutes freezing after cue	Insulin 0 (ng/ml)	<i>Biochemistry</i>		
	Faecal boli	Insulin 15(ng/ml)		Alkaline phosphatase (U/l)	
		Insulin 30 (ng/ml)		Alanine transaminase (U/l)	
<i>Fear potentiated startle</i>	Startle response	Insulin 75 (ng/ml)		Aspartate transaminase U/l)	
	Change in startle after training	DIRI/DG		Albumin (g/l)	
		AUC-IRI/AUC-G		Calcium (mmol)	
				Chloride (mmol)	
				Creatinine (mmol)	
				High density Lipoproteins (mmol)	

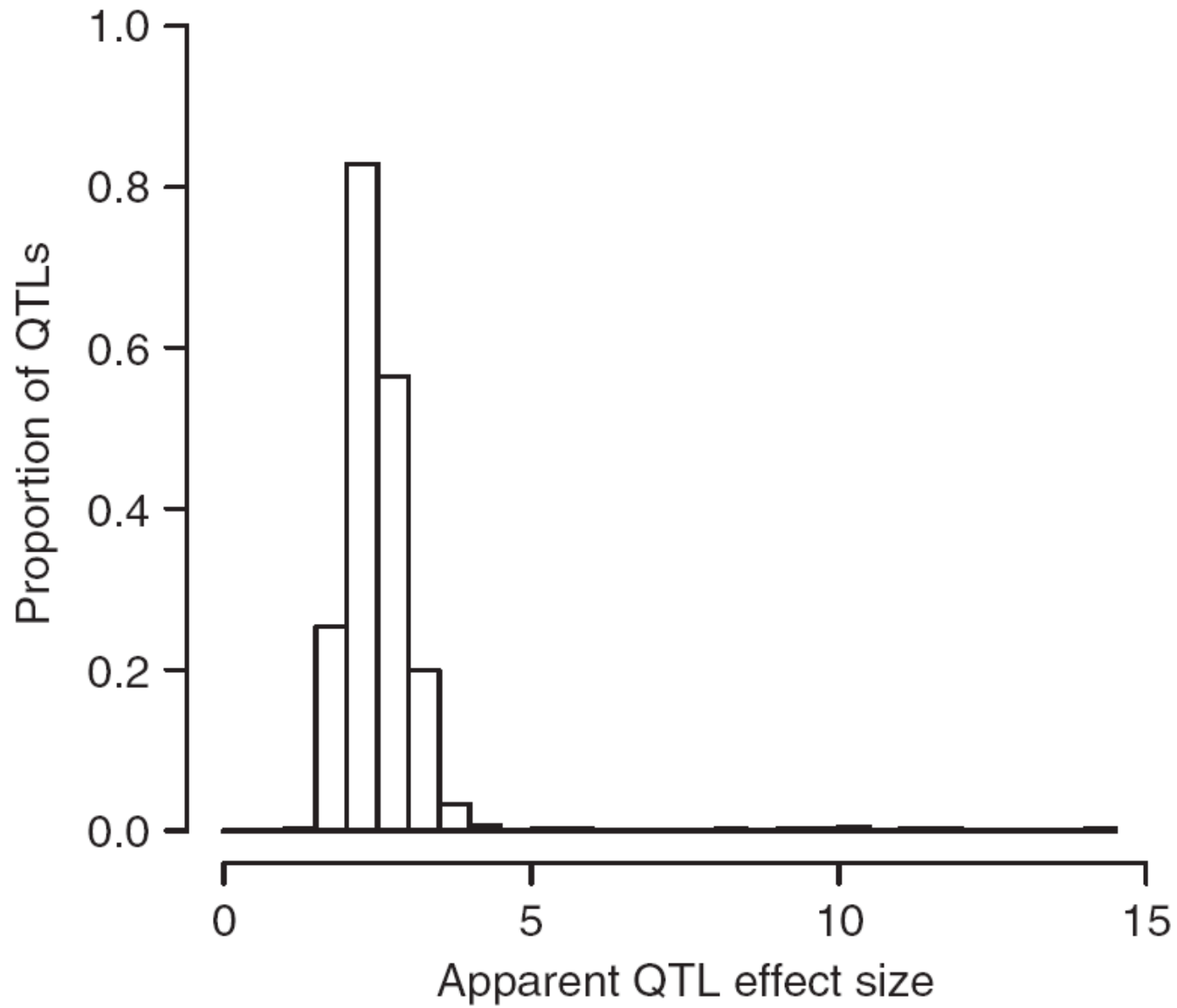
<http://gscan.well.ox.ac.uk>

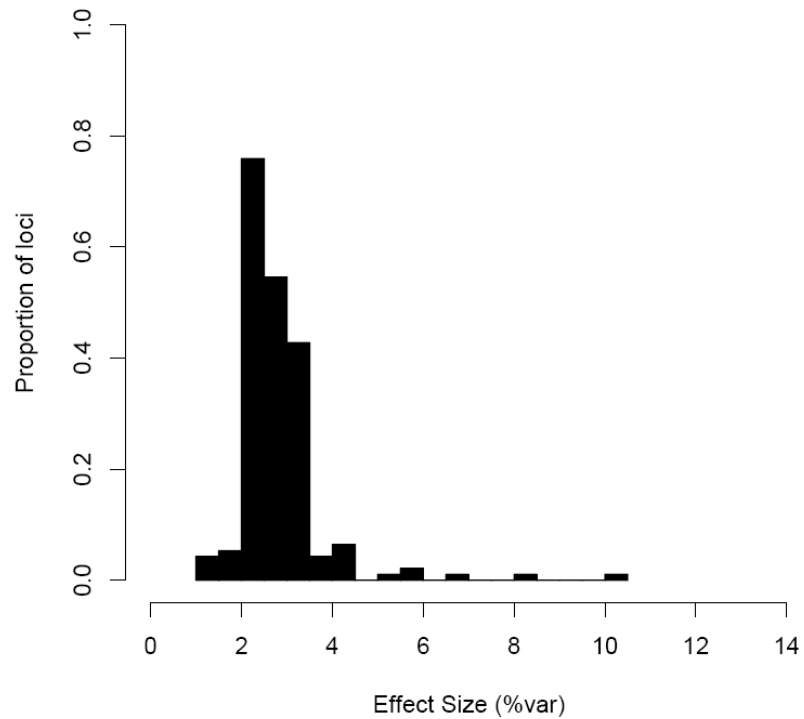


843 QTLs identified for 97 phenotypes

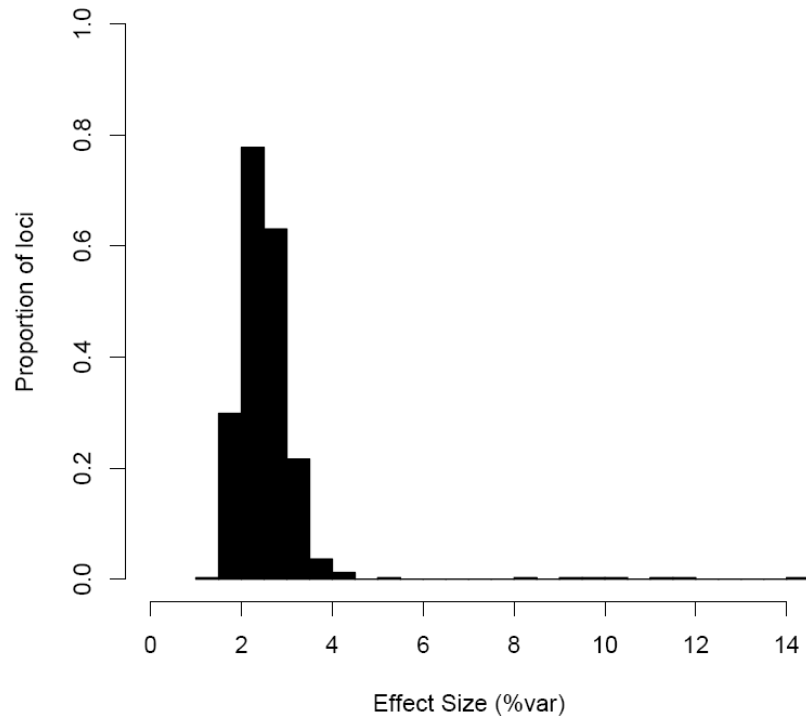
Genetic architecture

- Genetic effect sizes



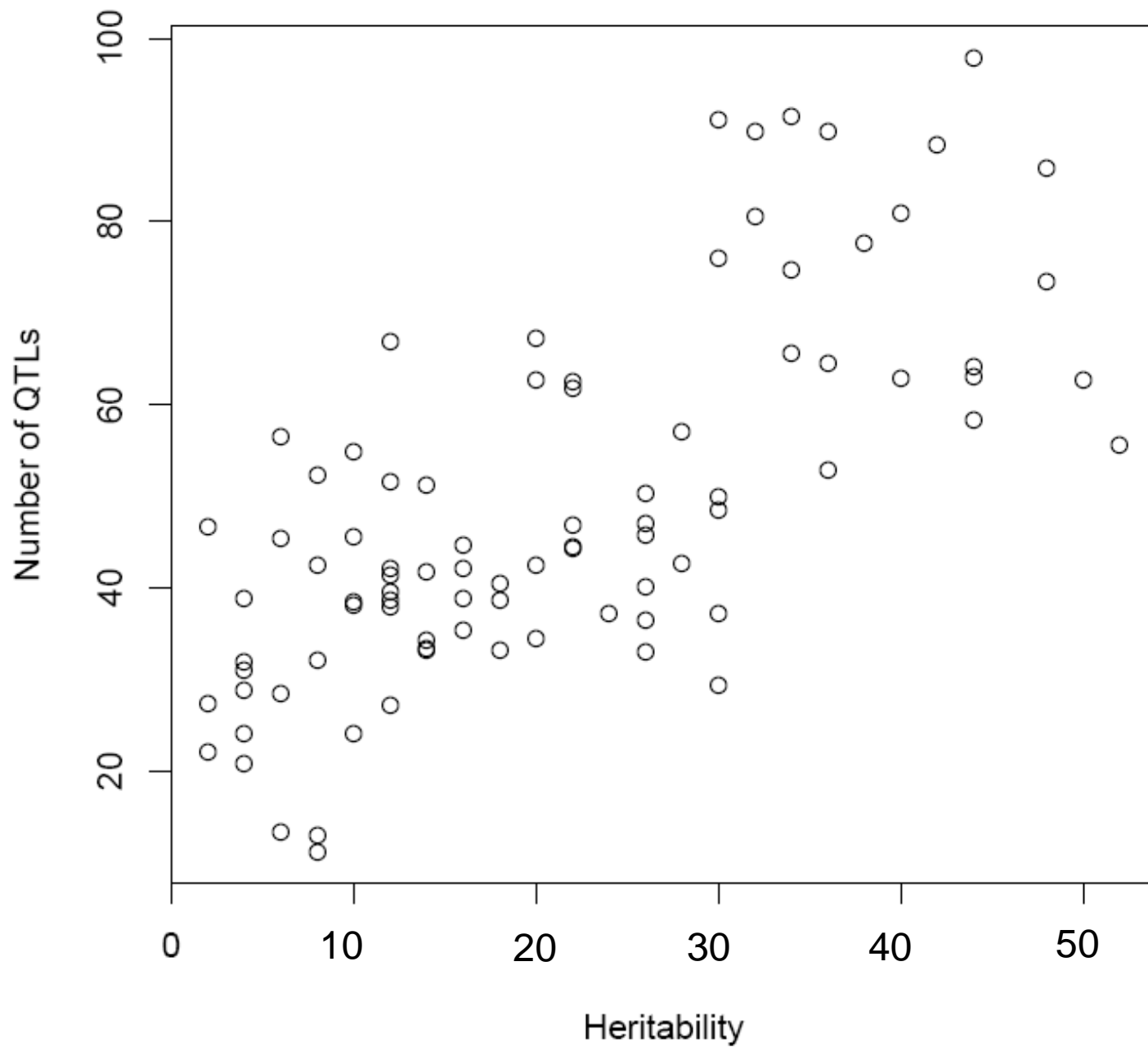


Behavioural QTLs

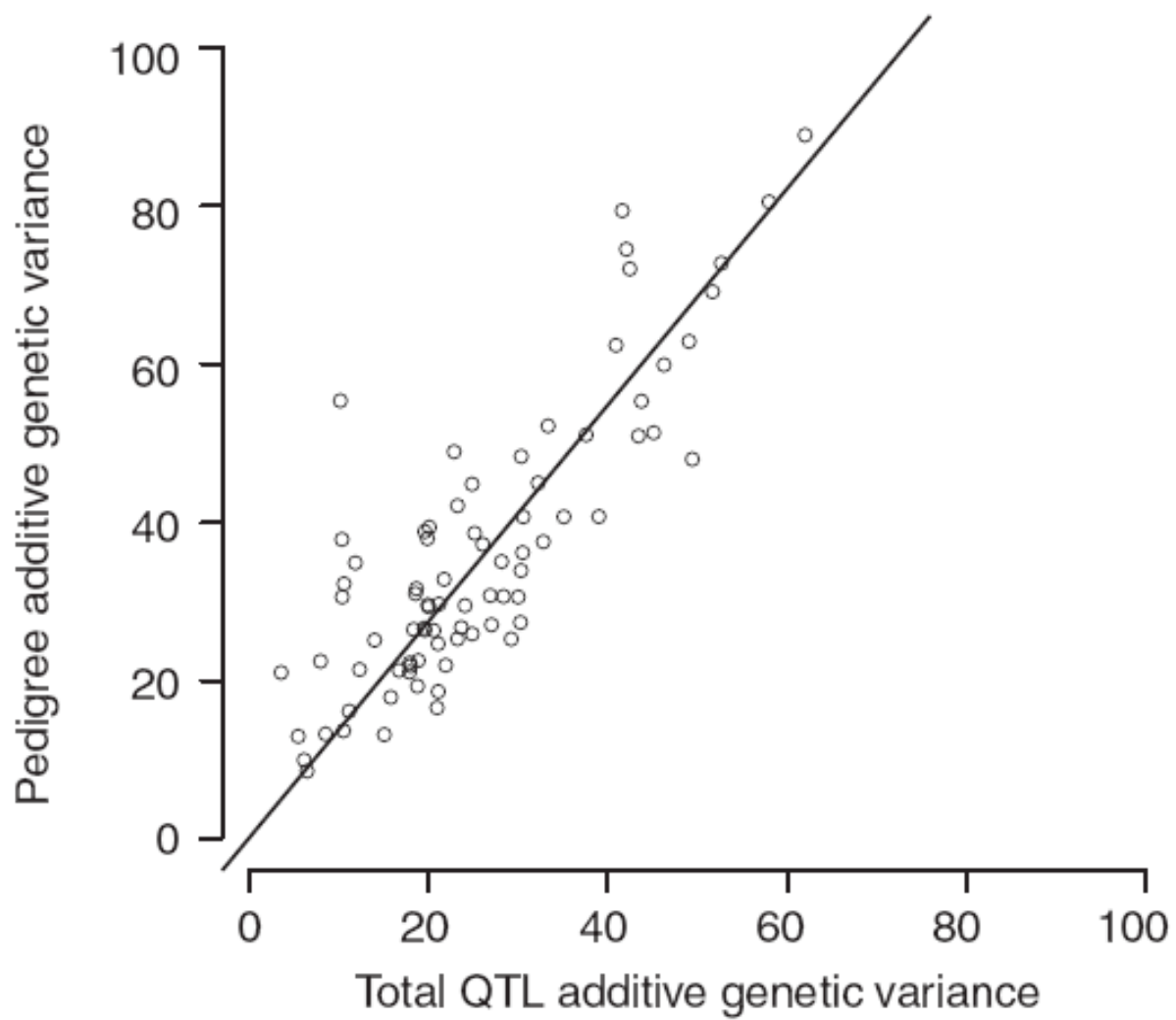


Non-Behavioural QTLs

- The distribution of QTL effect sizes is the same for all phenotypes



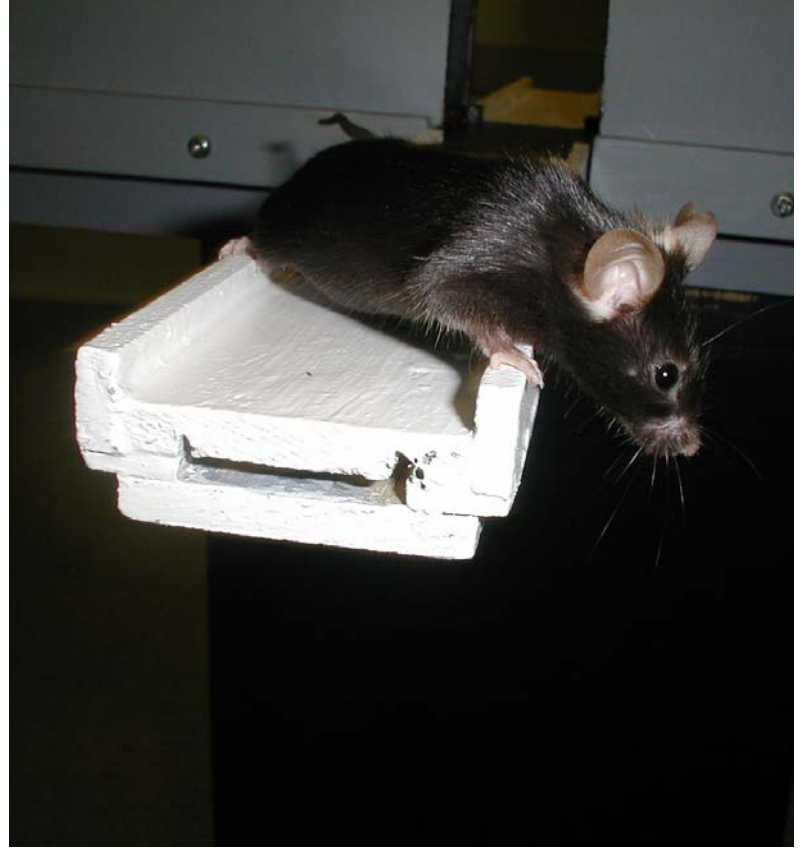
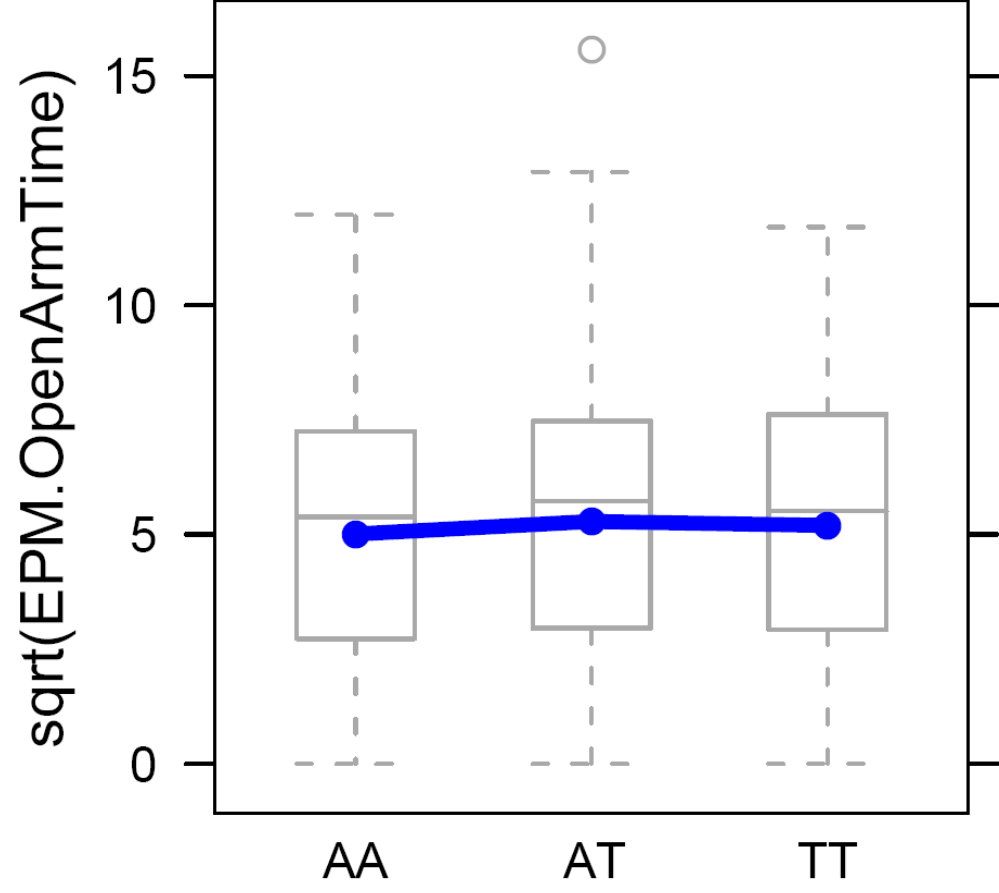
- The distribution of QTL effect sizes is the same for all phenotypes
- The number of QTLs detected correlates with the heritability

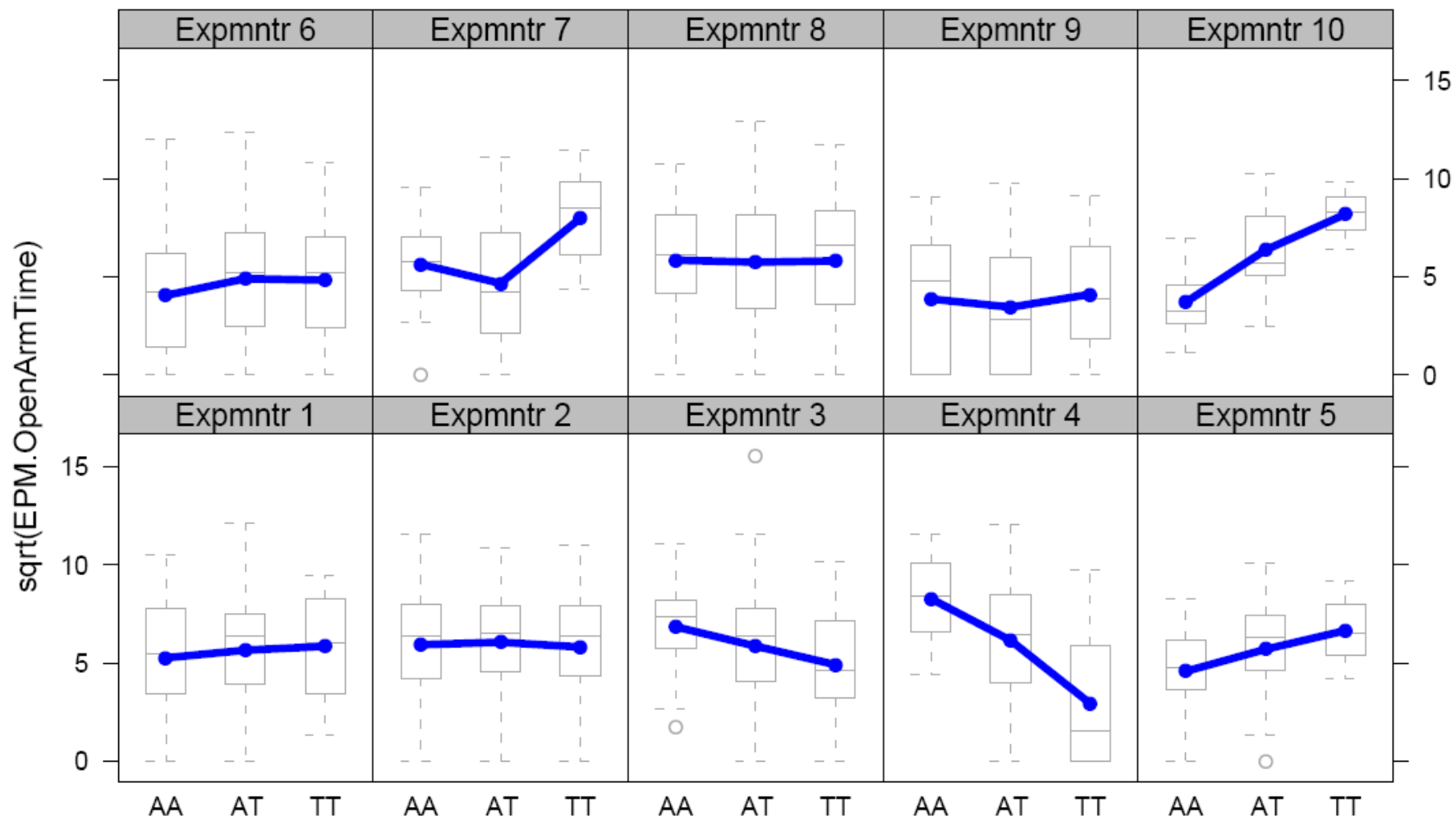


- The distribution of QTL effect sizes is the same for all phenotypes
- The number of QTLs detected correlates with the heritability
- Detected QTLs explain about 75% of the heritability

Genetic architecture

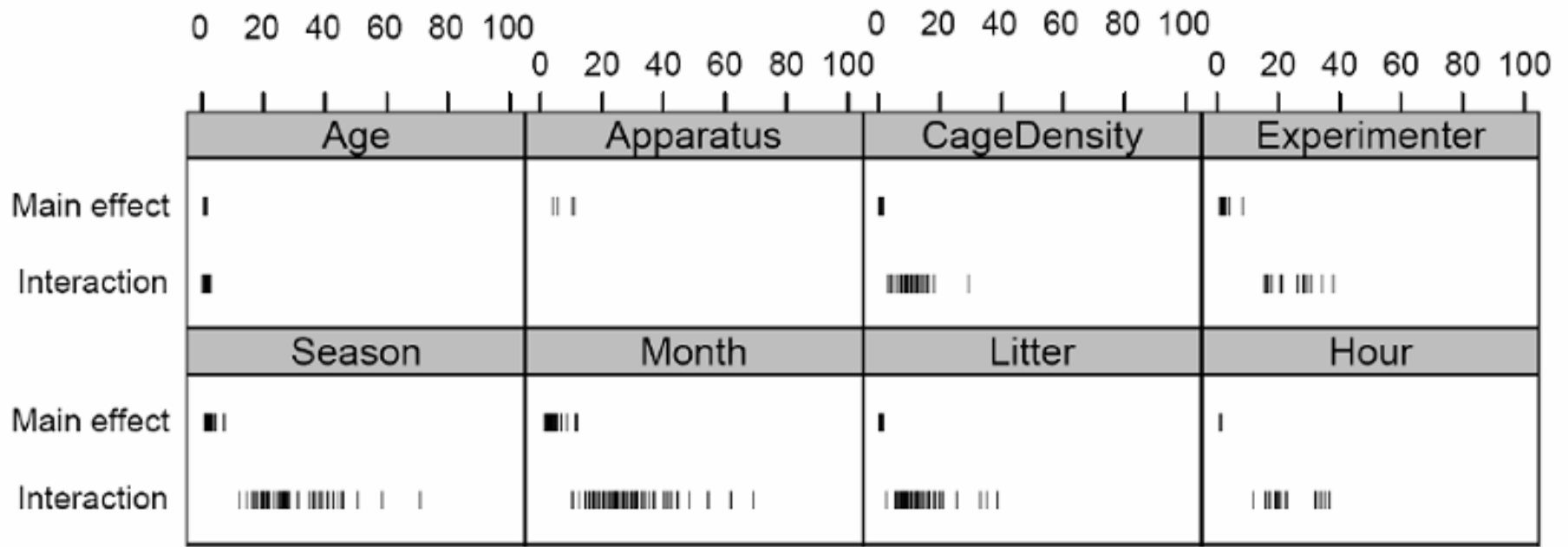
- Genetic effect sizes: small
- Environmental interactions





Covariates

- Age
- Apparatus
- Number of animals in a cage (cage density)
- Experimenter
- Litter size
- Season
- Month
- Hour



% variance explained by significant covariates

Genetic architecture

- Genetic effect sizes: small
- Environmental interactions: many
- Sex

Genetic architecture

- Genetic effect sizes: small
- Environmental interactions: many
- Sex: less than 20 sex-specific QTLs

Genetic architecture

- Genetic effect sizes: small
- Environmental interactions: many
- Sex: less than 20 sex-specific QTLs
- Epistasis

Genetic architecture

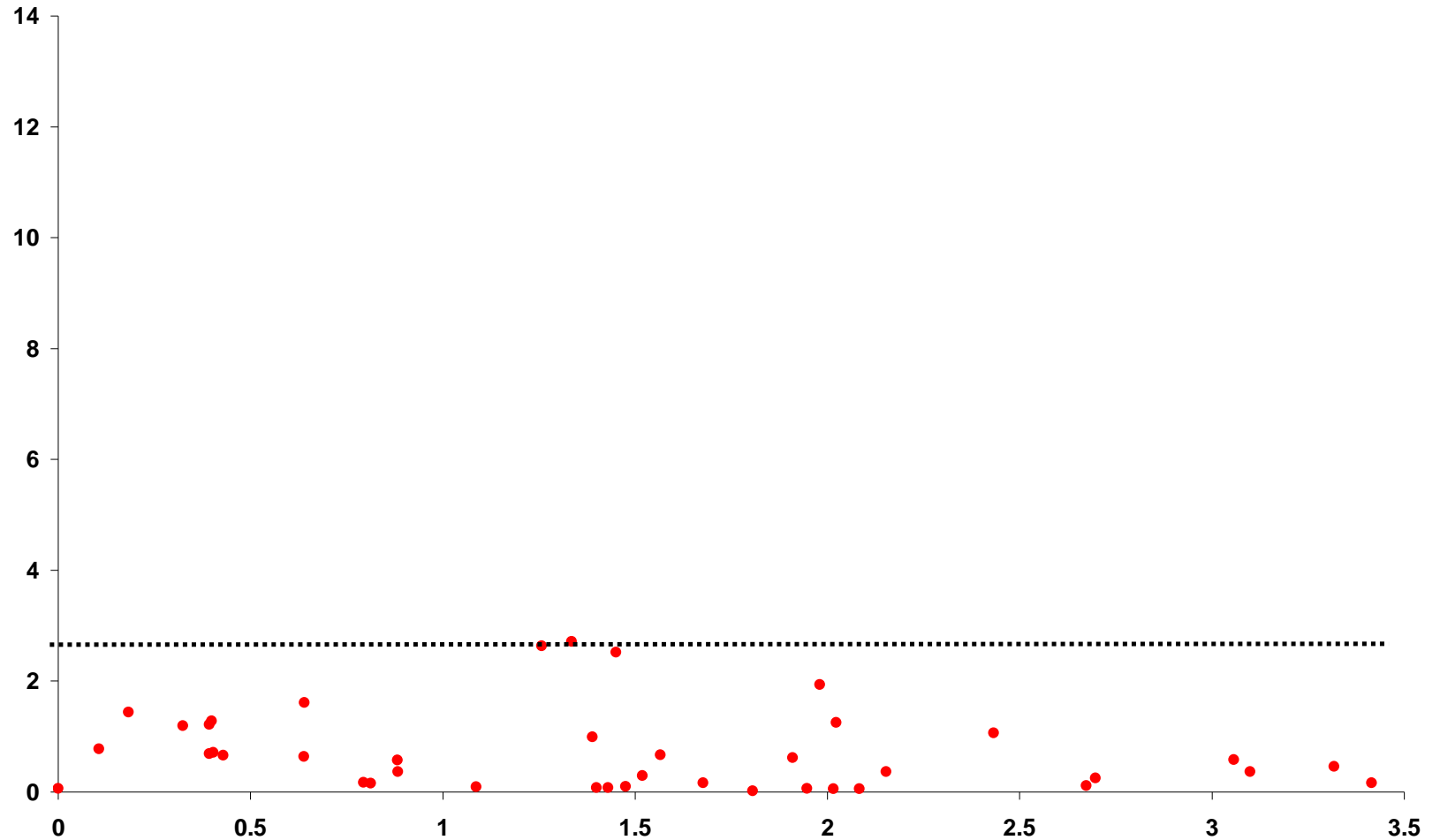
- Genetic effect sizes: small
- Environmental interactions: many
- Sex: less than 20 sex-specific QTLs
- Epistasis: probably not a lot

Outbreds

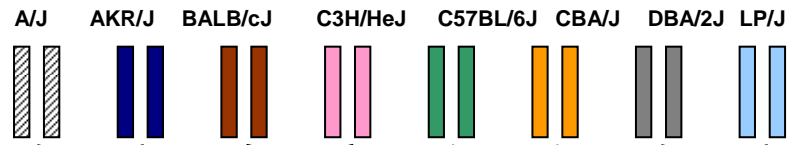
MF1 Mice



Analysis carried out by me



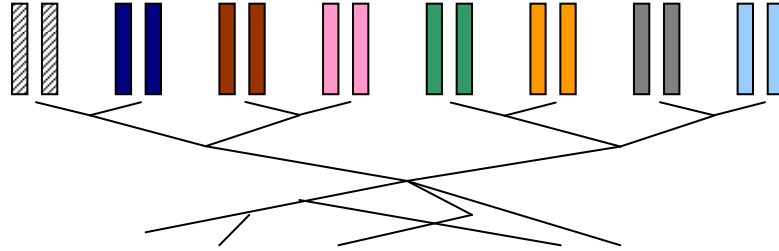
Heterogeneous stocks



Pseudo-random mating
for 50 generations



Outbred stocks





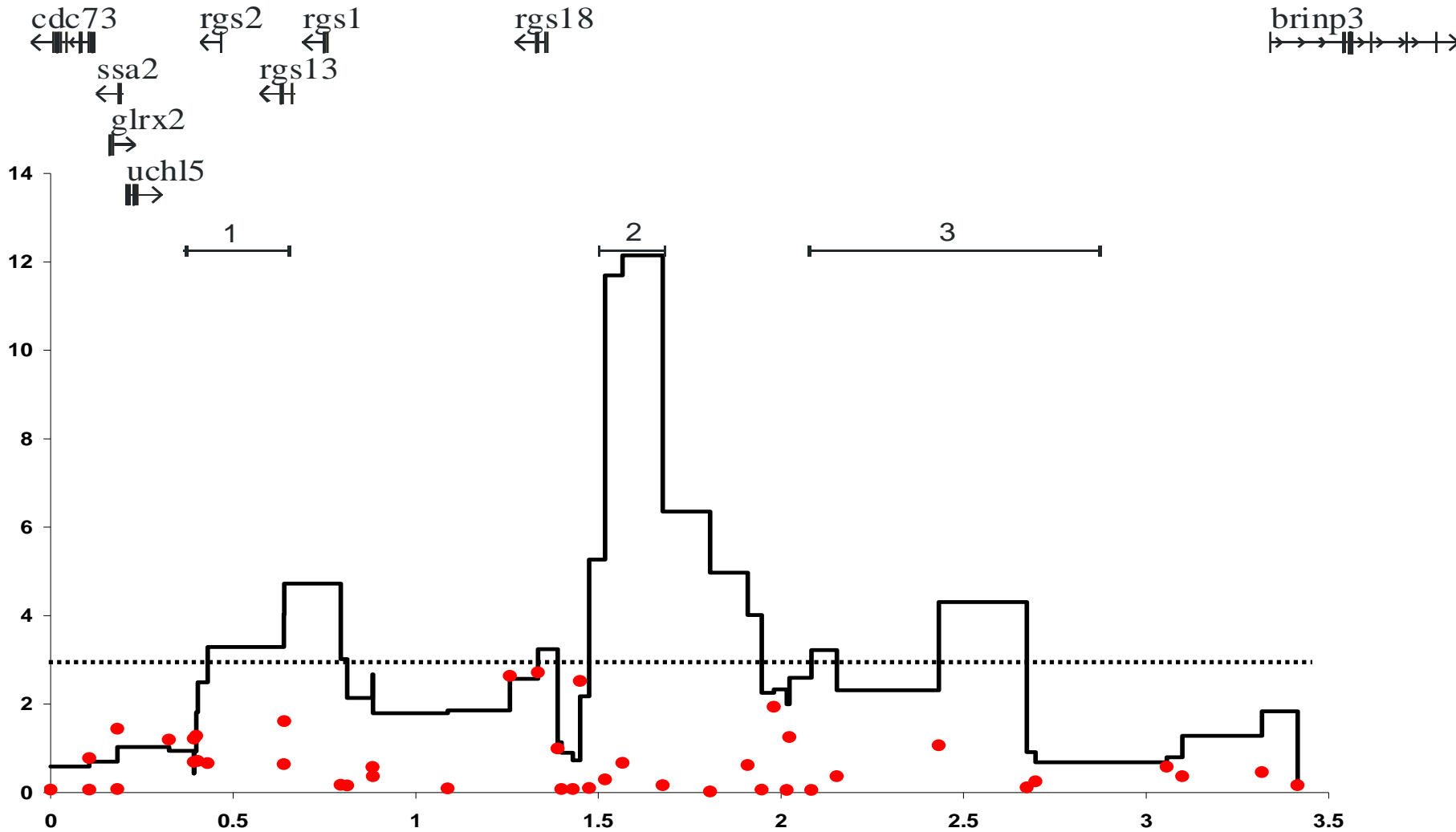
$$x_m(s, t) = \sum_{s', t'} x_{m-1}(s', t') \psi_m(s, t | s', t')$$

High resolution mapping in outbred mice

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

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

Analysis carried out by Richard



Approaches

- Collaborative cross
- In silico mapping
- Outbreds
- ENU/Knock outs

The roads from phenotypic variation to gene discovery: mutagenesis versus QTLs

Joseph H. Nadeau¹ & Wayne N. Frankel²

Overall, however, it is the successful identification of the genetic lesions that give rise to mutant phenotypes, compared with the ability to identify the variant that underlies naturally occurring QTLs, which makes mutagenesis the road of choice.

Neuroscience Mutagenesis Facility

2000 - 2006

[Available Strains](#)

[Strains Under Development](#)

[Not of Central Interest](#)

[All NMF Lines](#)

[Scientific Overview](#)

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[NMF Home](#)

The Neuroscience Mutagenesis Facility of the Jackson Laboratory (NMF) was established to produce new neurological mouse models that could serve as experimental models for the exploration of basic neurobiological mechanisms and diseases. The impetus for the program resulted from the recognition that **a**) the value of genomic data would remain limited unless more information about the functionality of its individual components became available, and **b**) the task of linking genes to specific behavior would best be accomplished by employing a combination of different approaches. In an effort to complement already existing programs, the Neuroscience Mutagenesis Facility decided to use: a random, genome-wide approach to mutagenesis, i.e. N-ethyl-N-nitrosourea (ENU) as the mutagen; a three-generation back-cross breeding scheme to focus on the detection of recessive mutations; behavioral screens selective for the detection of phenotypes deemed useful for the program goals.

The resulting mutant mouse lines have been available to the scientific community for the last five years and over 700 NMF mice have been sent to interested investigators for research; these mutant mouse lines will remain available as frozen embryos (which can be re-derived on request) and can be ordered through the JAX customer service at 1-800-422-6423 (or 207-288-5845). The results of the work of the Neuroscience Mutagenesis Facility and that of two other neurogenesis centers, i.e. The Neurogenomics Project at Northwestern University, and the Neuromutagenesis Project of the Tennessee Mouse Genome Consortium, can also be seen at Neuromice.org, a common web site of these three research centers; in addition, information about all mutants produced by these groups has been recorded in [MGI](#).

The work of these three research centers has been made possible through grants from The National Institute of Neurological Disorders and Stroke, The National Institute of Drug Abuse, The National Institute of Mental Health, The National Institute of Deafness and Other Communication Disorders, The National Institute of Aging, The National Eye Institute, and The National Institute of Alcohol Abuse and Alcoholism and was supported through August 2006.

Neuroscience Mutagenesis Facility

2000 - 2006

[Available Strains](#)

[Strains Under Development](#)

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NIH Neurogenomics Project at Northwestern University

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The NIH Neurogenomics Project at Northwestern University

[Contact](#)

[Center for Functional Genomics at Northwestern University](#)

[National Institutes of Health](#)

Directed by [Dr. Joseph Takahashi](#), the NIH Neurogenomics Project at Northwestern University is dedicated to furthering functional genomics research, by utilizing phenotype-driven, or forward genetics, techniques to identify genes.

Background

The [National Institutes of Health \(NIH\)](#) have recognized the importance of phenotype-driven approaches in bridging the gap between gene identification and understanding gene function. Knowledge of the genetics of nervous system function and regulation of behavior will lead to improved understanding of normal and abnormal brain function and behavior, enhanced diagnostics, and more effective therapeutics. The NIH Neurogenomics Project at Northwestern University is one of three Centers funded by NIH to use forward genetic strategies to identify genes involved in nervous system function and behavior.

Objective

Established in 2001, the overall objective has been to use ENU-mutagenized C57BL/6J mice to identify neurobehavioral mutations in five domains. The project uses a three-generation breeding scheme to produce homozygous mutants to recover both recessive and dominant mutations. Phenotypic screens focus on five primary domains: neuroendocrine and behavioral responses to stress, learning and memory, psychostimulant response, vision, and circadian rhythm.



Neuroscience Mutagenesis Facility

2000 - 2006

The Neuroscience Mutagenesis Facility of the Jackson Laboratory (NMF) was established to produce new neurological mouse models that could serve as experimental models for the exploration of basic neurobiological mechanisms and diseases. The impetus for the program resulted from the recognition that a) the value of genomic data would remain

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Directed by [Dr. Joseph Takahashi](#), the NIH Neurogenomics Project at Northwestern University is dedicated to furthering functional genomics research, by utilizing phenotype-driven, or forward genetics, techniques to identify genes.

Harwell Mutagenesis Programme Website



Welcome to the Harwell Mutagenesis Programme

The purpose of the current mutagenesis programme is to generate and make available approximately 100 F1 progeny of mutagenised animals per week for genome-wide dominant phenotypic screens. Mice with aberrant phenotypes identified in any of the internal or collaborative phenotypic screens will be posted regularly on our website and will be made available to the scientific community.

This website will allow you to search the information gathered by the programme. Please use the links on the left to navigate the site. Any problems/Questions please use the feedback form to contact us.

Navigation Menu

- [HMP Home](#)
- [Description of Programme](#)
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Specific developmental disruption of disrupted-in-schizophrenia-1 function results in schizophrenia-related phenotypes in mice

Weidong Li^{*†‡§}, Yu Zhou^{*†‡§}, J. David Jentsch[§], Robert A. M. Brown^{*†‡§}, Xiaoli Tian[¶], Dan Ehninger^{*†‡§}, William Hennahl, Leena Peltonen, Jouko Lönnqvist^{**}, Matti O. Huttunen^{**}, Jaakko Kaprio^{**}, Joshua T. Trachtenberg[§], Alcino J. Silva^{*†‡§††}, and Tyrone D. Cannon^{†‡§}

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ARTICLES

Cortico-striatal synaptic defects and OCD-like behaviours in *Sapap3*-mutant mice

Jeffrey M. Welch^{1*}, Jing Lu^{1,4*}, Ramona M. Rodriguiz², Nicholas C. Trotta¹, Joao Peca^{1,5}, Jin-Dong Ding⁶, Catia Feliciano^{1,7}, Meng Chen³, J. Paige Adams⁸, Jianhong Luo⁴, Serena M. Dudek⁸, Richard J. Weinberg⁶, Nicole Calakos^{1,3}, William C. Wetsel² & Guoping Feng¹

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Social amnesia in mice lacking the oxytocin gene

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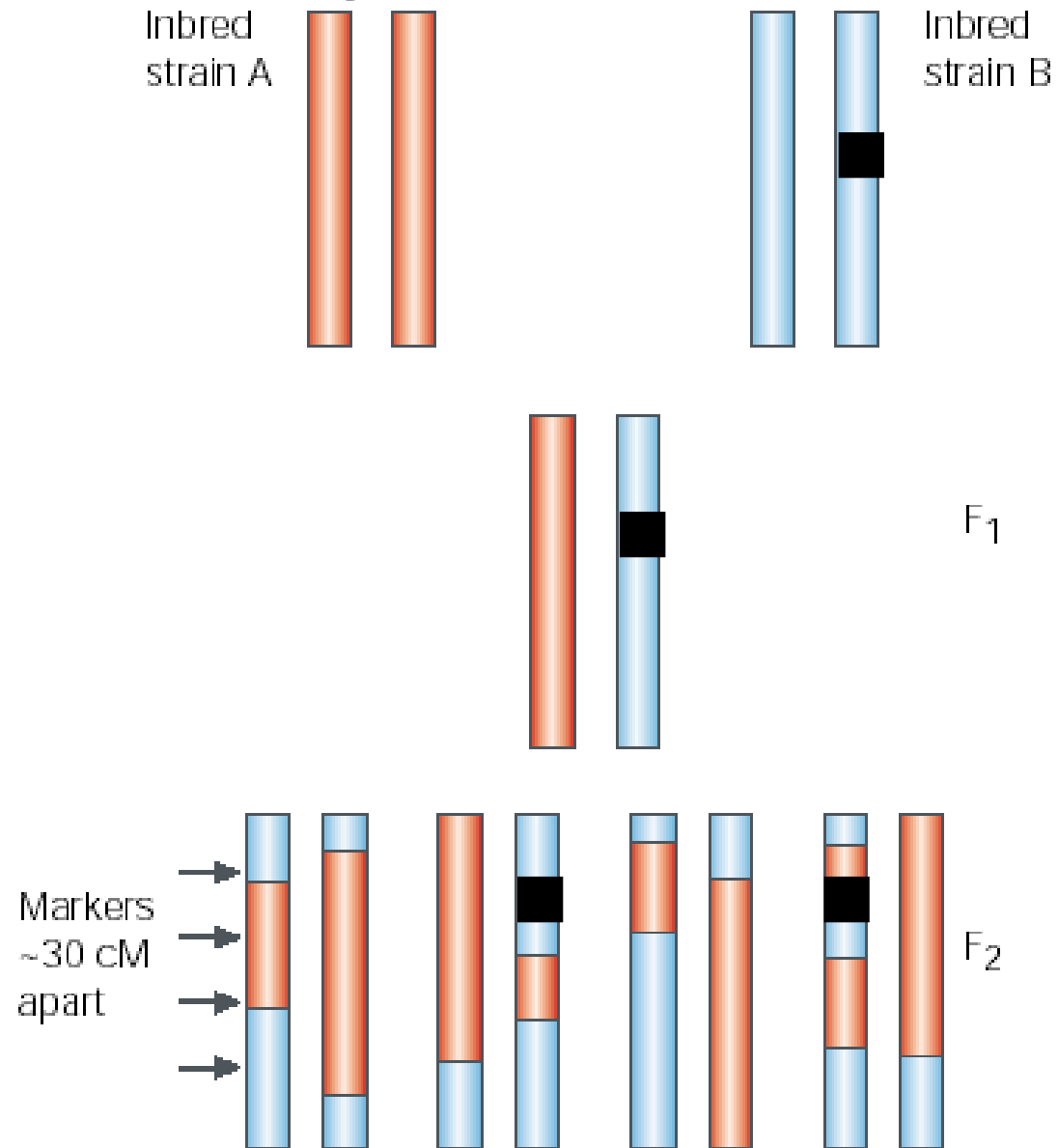
Mania-like behavior induced by disruption of *CLOCK*

Kole Roybal^{*}, David Theobald^{*}, Ami Graham^{*}, Jennifer A. DiNieri[†], Scott J. Russo^{*}, Vaishnav Krishnan^{*}, Sumana Chakravarty^{*}, Joseph Peevey^{*}, Nathan Oehrlein[‡], Shari Birnbaum^{*}, Martha H. Vitaterna[§], Paul Orsulak[‡], Joseph S. Takahashi[¶], Eric J. Nestler^{*}, William A. Carlezon, Jr.[†], and Colleen A. McClung^{*||}

^{*}Department of Psychiatry and Center for Basic Neuroscience, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9070; [†]Behavioral Genetics Laboratory, Department of Psychiatry, McLean Hospital, Harvard Medical School, MRC 217, 115 Mill Street, Belmont, MA 02478; [‡]Pathology and Laboratory Medicine Service, Veterans Affairs North Texas Health Care System, 4500 South Lancaster Road, Dallas, TX 75216; [§]Center for Functional Genomics and Department of Neurobiology and Physiology, Northwestern University, Evanston, IL 60208; and [¶]Howard Hughes Medical Institute, Department of Neurobiology and Physiology, Northwestern University, Evanston, IL 60208-3520

Edited by Michael Rosbash, Brandeis University, Waltham, MA, and approved February 8, 2007 (received for review October 30, 2006)

Mapping ENU mutants



What is the effect size of a mutant on behaviour?

What is the effect size of a mutant on behaviour?

~10-20%

$$\left(\frac{1 - V_{\text{QTL}}}{V_{\text{QTL}}} \right) \left(\frac{Z_{1-\alpha/2}}{(1 - V_{\text{QTL}})^{1/2}} + Z_{1-\beta} \right)^2$$

Effect size	Number of Animals
2	1350
4	682
5	549
10	282
15	194
20	151
21	145
22	139
23	134
24	130
25	125

Table 1. International Mouse Gene Knockout Programs

Type of Resource	Type of Knockout	2006	2007	2008	2009	2010	Totals
KOMP							
ES Cell	Targeted Deletion	175	500	941	942	942	3500
Mouse	Targeted Deletion	50	50	50	50	50	250
ES Cell	Targeted Conditional	1000	1000	1000	1000	1000	5000
Mouse	Targeted Conditional	50	50	50	50	50	250
EUCOMM							
ES Cell	Trapped Conditional	3000	6000	3000			12,000
ES Cell	Targeted Conditional	1000	3000	4000			8000
Mouse	Mixed	20	100	200			320
NorCOMM							
ES Cell	Trapped Conditional	1000	4000	3000	2000		10,000
ES Cell	Targeted Conditional	100	400	750	750		2000
Mouse	Mixed	25	25	25	25		100
Cumulative for All Programs							
ES Cell	Trapped (Conditional)	4000	14000	20000	22000		22,000 ^a
ES Cell	Targeted (Deletion)	175	675	1616	2558	3500	3500
ES Cell	Targeted (Conditional)	2100	6500	12,250	14,000	15,000	15,000
Mouse	Mixed	125	400	715	830	920	920

Cell 128, January 12, 2007

Deltagen and Lexicon

Phenotype	No. Sig (P <0.05)	Pct.	Total
Open Field Activity	39	18.9	206
Albumin	18	7.1	254
Alkaline phosphatase	18	7.1	254
Blood urea nitrogen	23	9.1	254
Calcium	16	6.3	254
Cholesterol	26	10.2	254
Glucose	10	3.9	254
Hemoglobin	11	4.5	243
Phosphorous	18	7.1	254
Platelets	14	5.8	243
Triglycerides	17	6.7	254
White blood cells	15	6.2	243

Approaches

- Collaborative cross
- In silico mapping
- Outbreds
- ENU/Knock outs

Work of many hands

- Carmen Arboleda-Hitas
- Amarjit Bhomra
- Peter Burns
- Richard Copley
- Stuart Davidson
- Simon Fiddy
- Polinka Hernandez
- Guo-Jen Huang
- David Keays
- Sue Miller
- Richard Mott
- Chela Nunez
- Sagiv Shifman
- Leah Solberg
- Amy Taylor
- Martin Taylor
- Jen Taylor
- Jordana Tzenova-Bell
- William Valdar
- Binnaz Yalcin
- Dave Bannerman
- Christophe Benoist
- Shoumo Bhattacharya
- Bill Cookson
- Rob Deacon
- Doug Higgs
- Tertius Hough
- Paul Klenerman
- Dominique Gauguier
- Nick Rawlins
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