

From biomarkers to drug targets: genetic animal models of stress and psychiatric disorders

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Animal models

Behavior

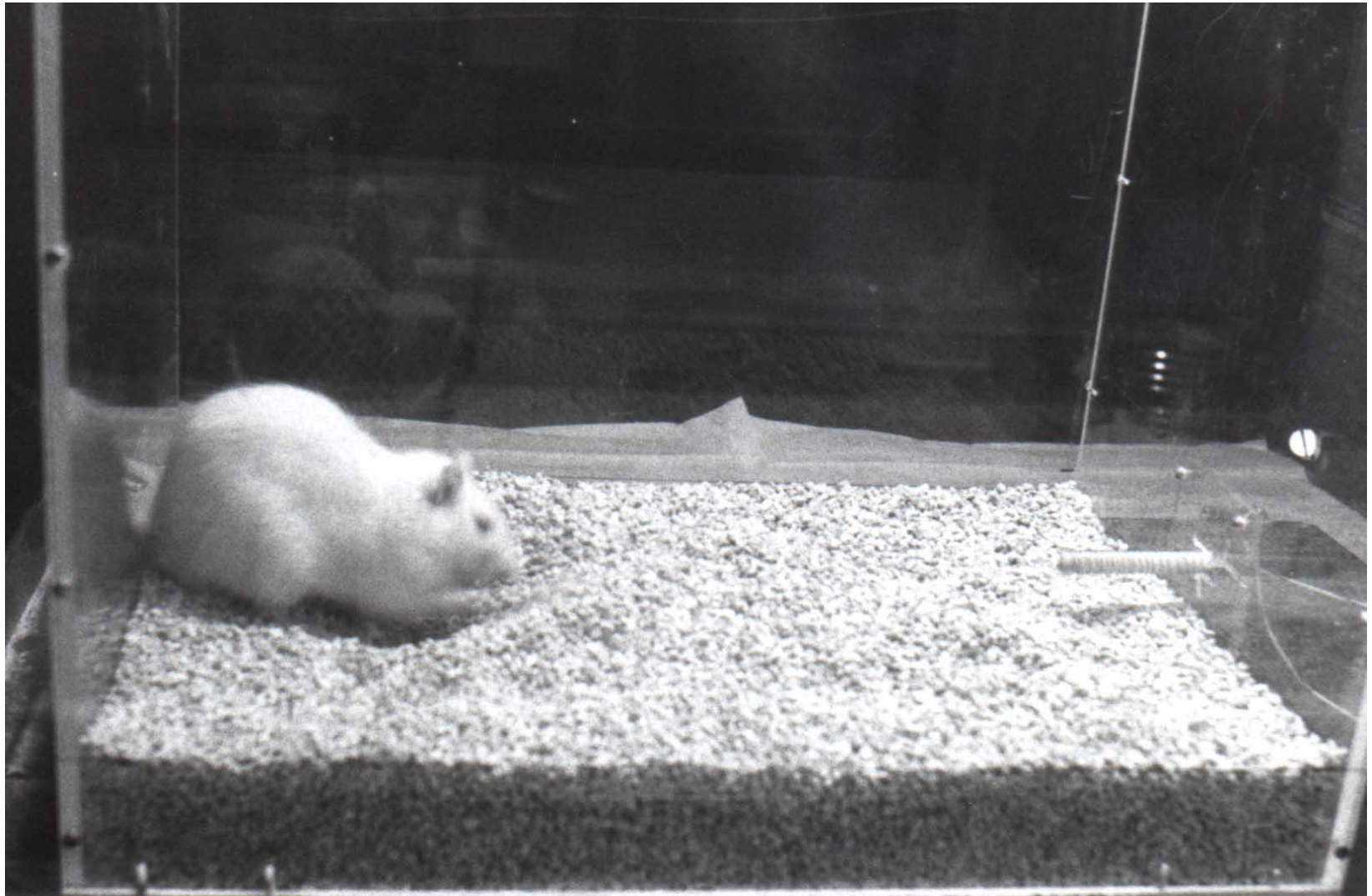
- Defensive Burying
- Elevated Plus Maze
- Light-Dark Box
- Social interaction
- Forced Swim Test
- Morris Water Maze
- Object recognition

Genetics, transcriptomics

- DNA or RNA
- How to collect samples
- Genotyping
- Microarrays
- Analyses
- Quantitative RT-PCR

WKY Rat – depressive and/or anxiety-like behavior in several tests

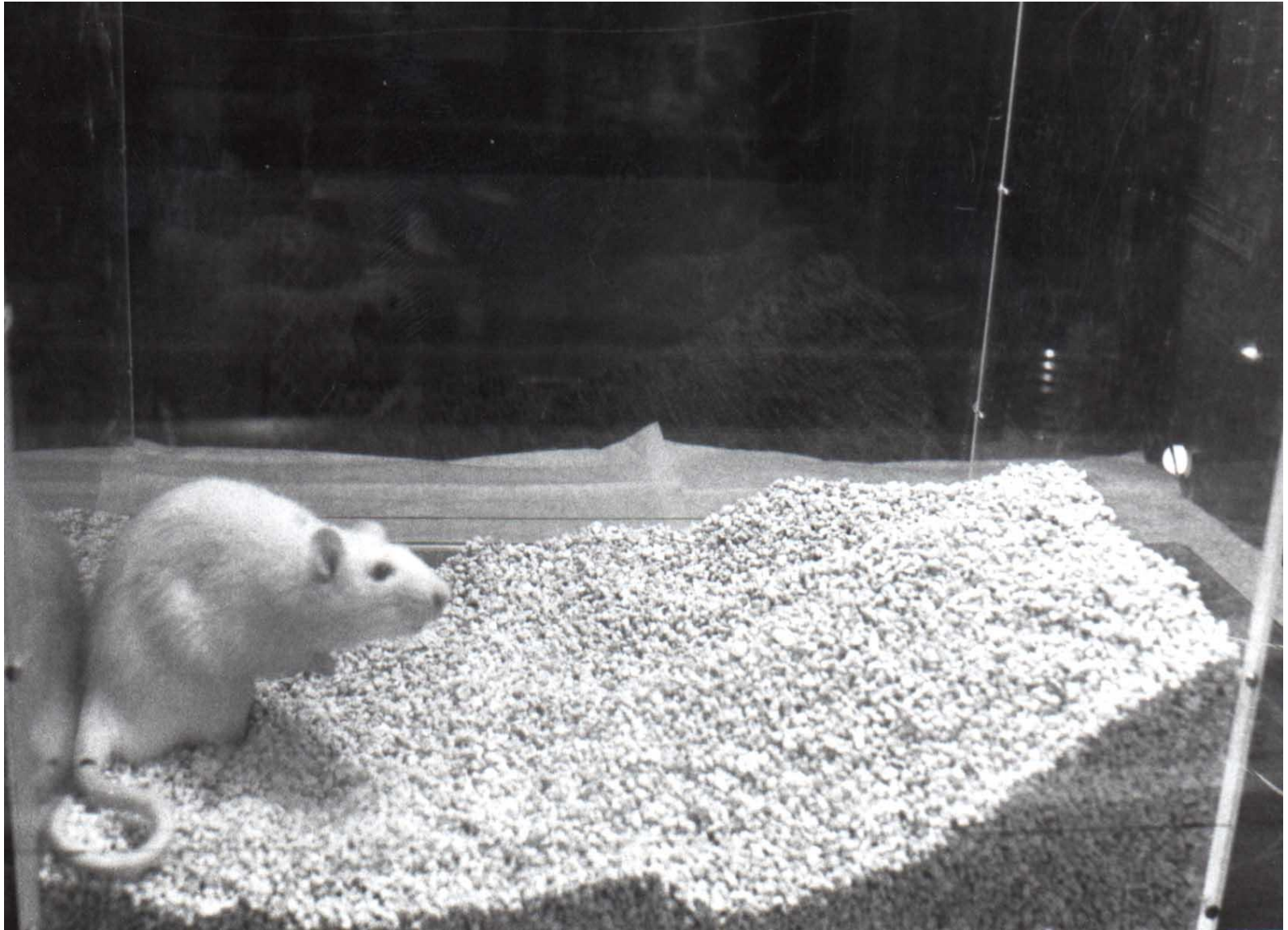
- Forced Swim Test
 - Learned Helplessness
 - Open Field Test
 - Elevated Plus Maze
 - Defensive Burying
 - Light/Dark box
 - Open field Arena
-
- ↑ immobility
↓ escape behavior
↓ exploration
↓ decision
↑ passive coping
↑ ambivalence
↓ feeding



Neuroendocrinology Symposium,
Istanbul, 2009



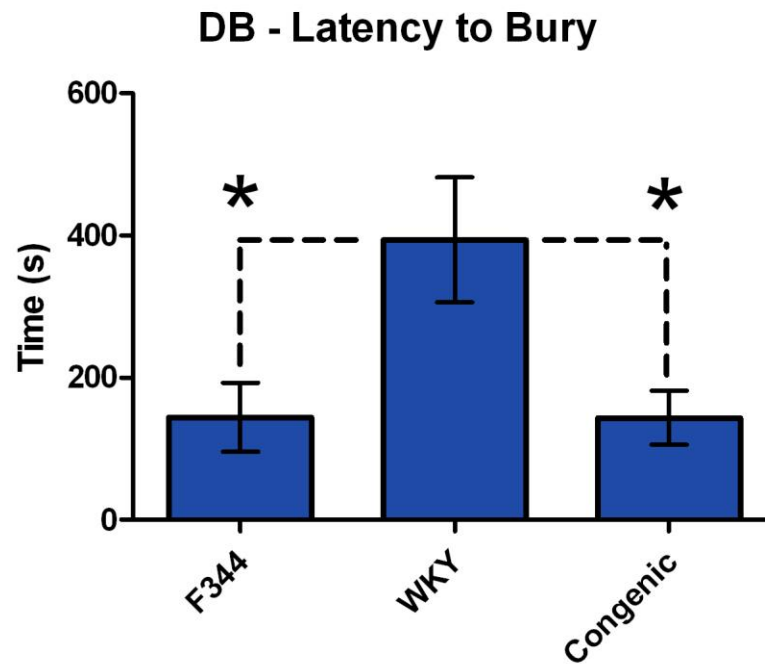
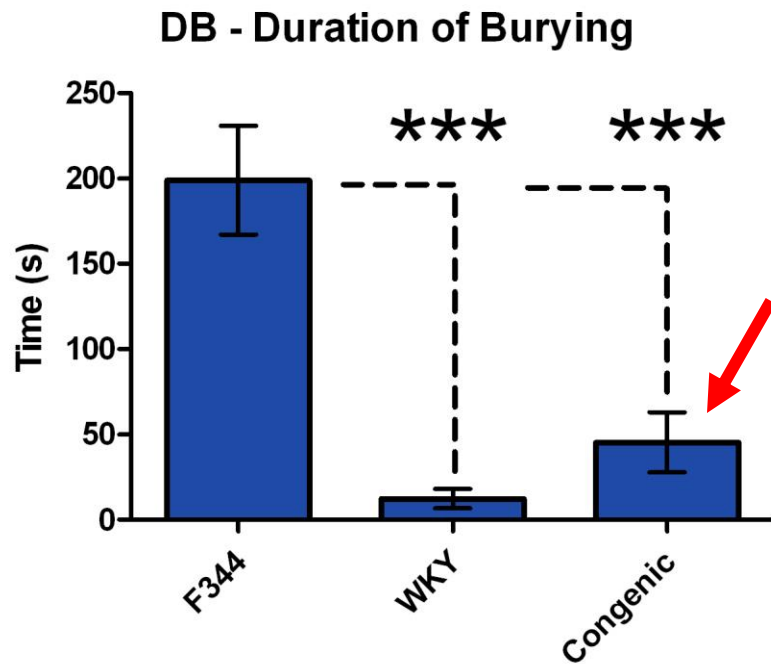
Neuroendocrinology Symposium,
Istanbul, 2009



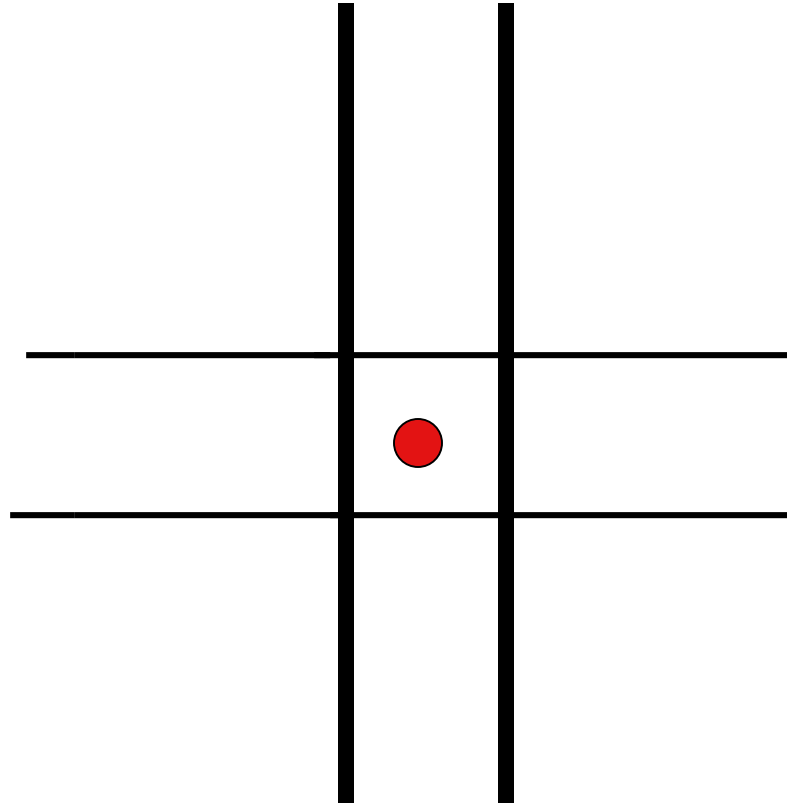
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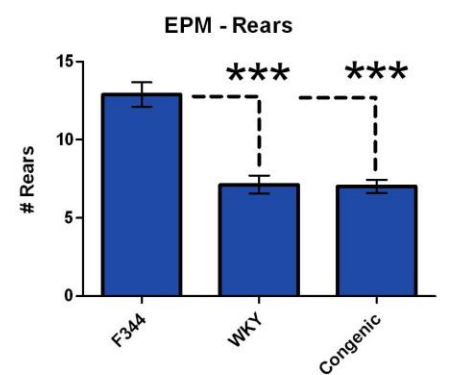
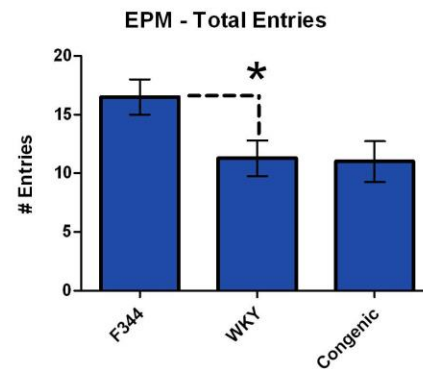
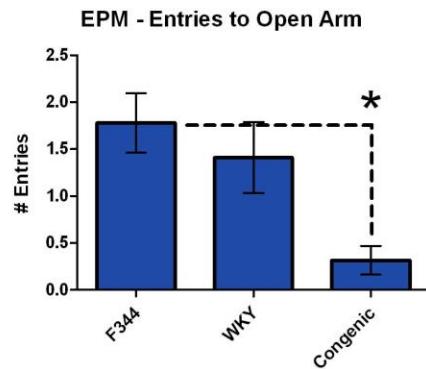
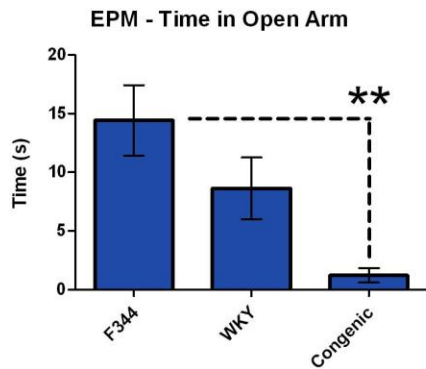
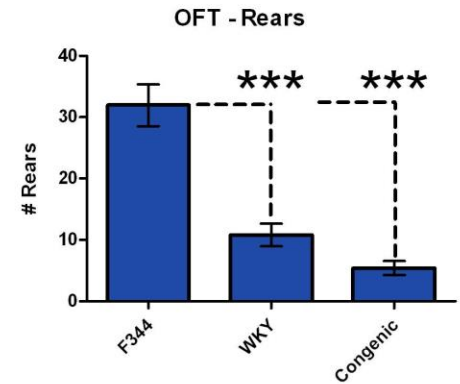
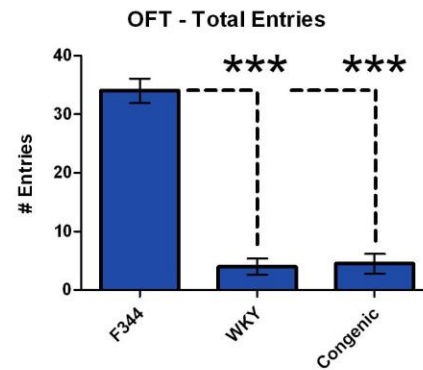
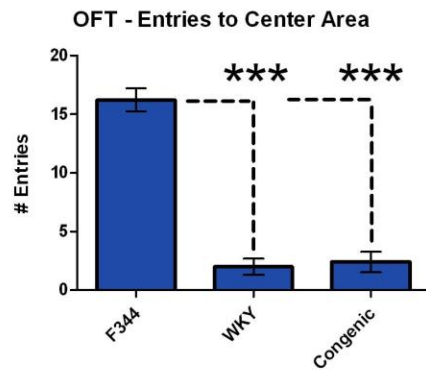
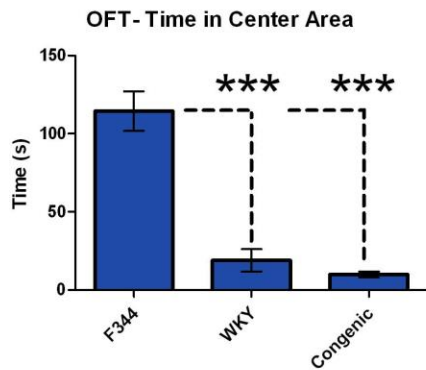
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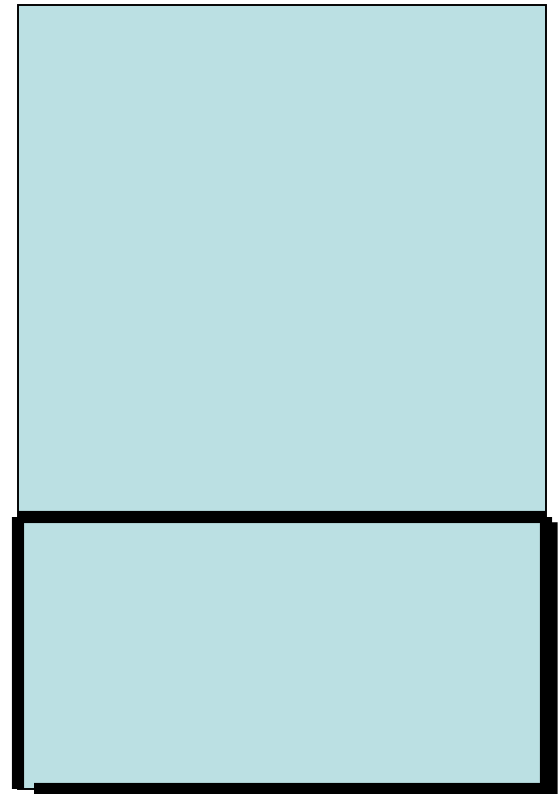
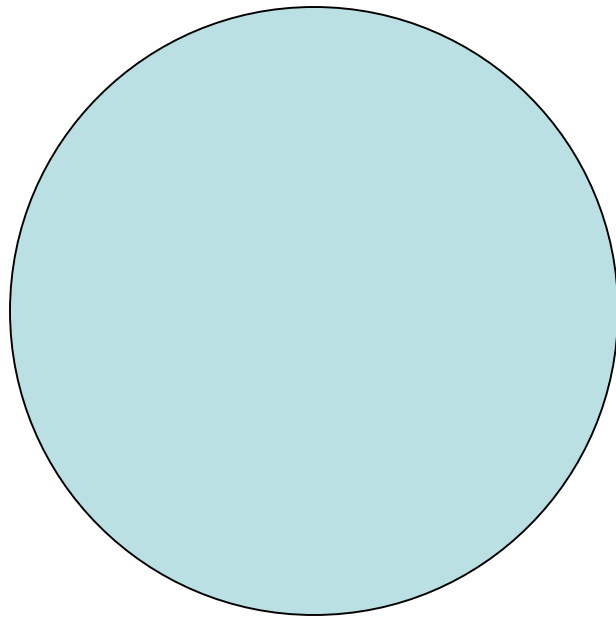
Elevated Plus Maze



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Open Field Test and Light Dark Box



Social Interaction

The animal to be studied and a subject animal: different age or gender

Olfactory investigation of subject 1

Olfactory Investigation of subject 2

Difference in time spent in olfactory investigation: social recognition

Object Recognition

Two objects of the same size and shape and color

Different object at the place of the second object

Repeat

Same objects at different place

Measure: investigation of the familiar object
 investigation of the unfamiliar object
 investigation of the familiar object at different place

Animal models

Behavior

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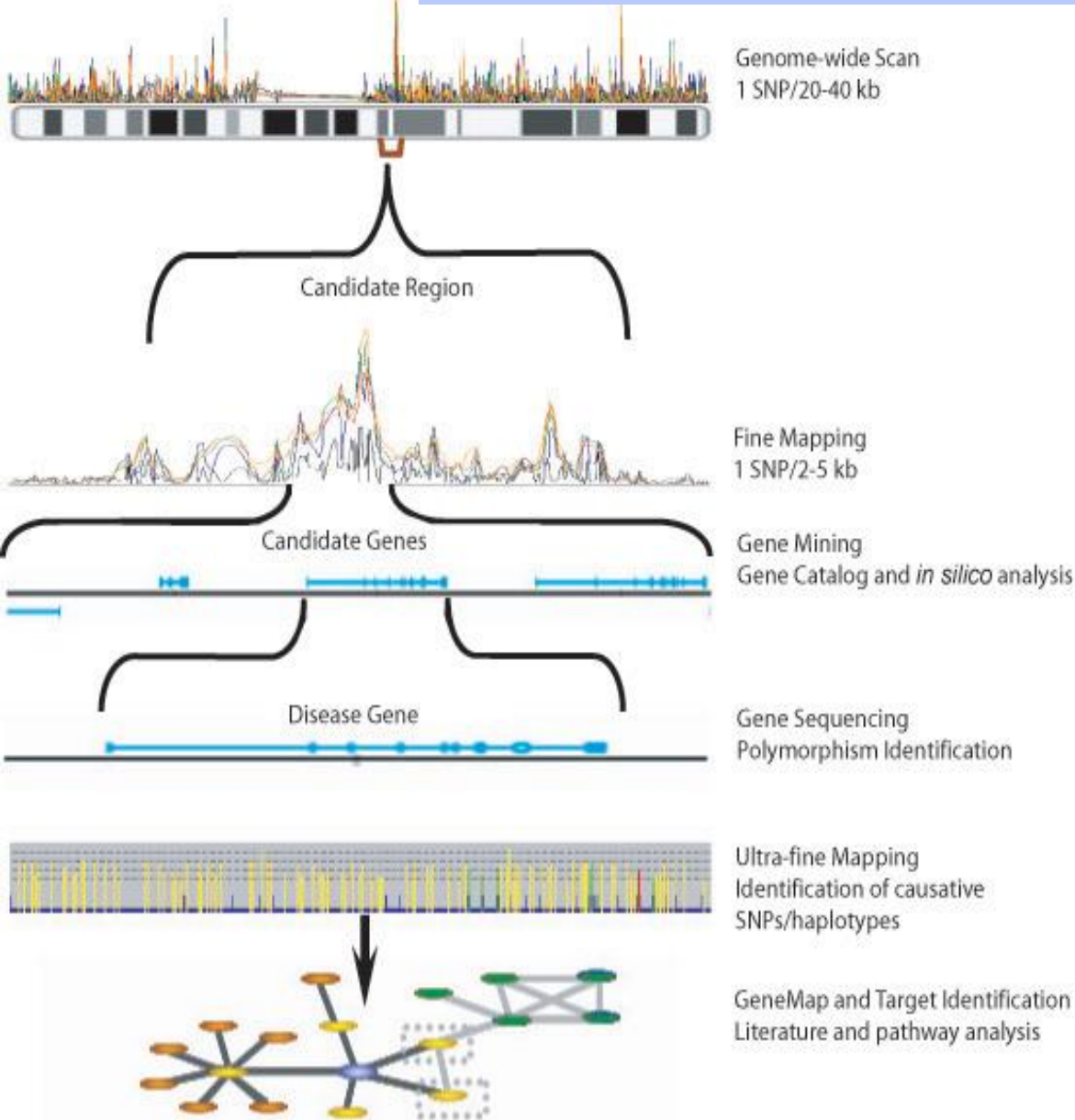
Genetics, transcriptomics

- DNA or RNA
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DNA

- Isolation of DNA
- Different sources of DNA
- Amplification of DNA
- SNP or Marker

Human genetic studies of complex disorders are difficult



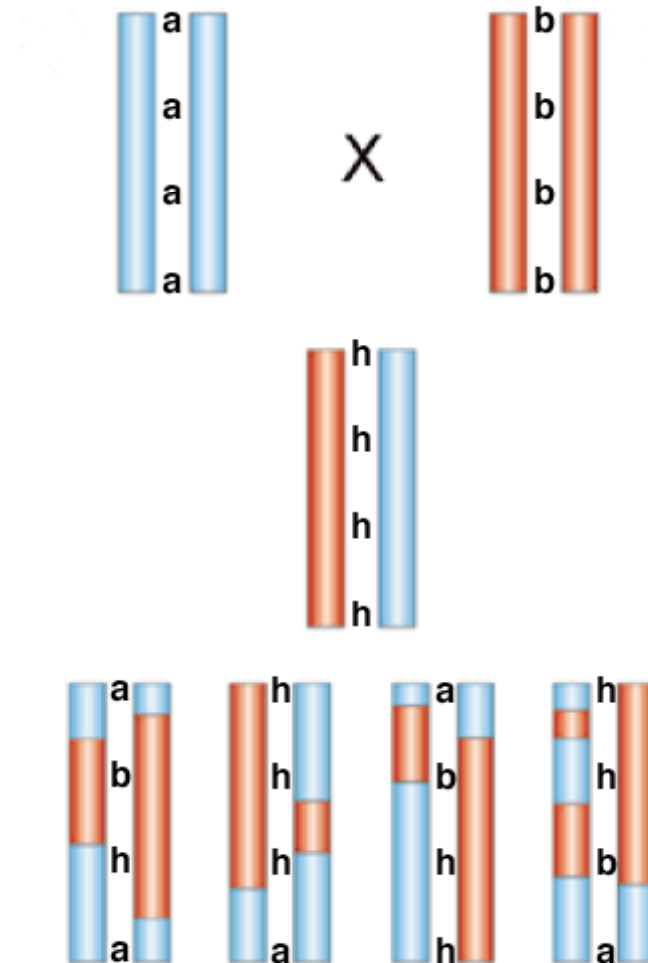
*DNA samples from a large population that is properly diagnosed. Without an easy laboratory test it is **HARD**.*

*Single Nucleotide Polymorphism (**SNP**) markers, on microchip: **THAT IS EASY***

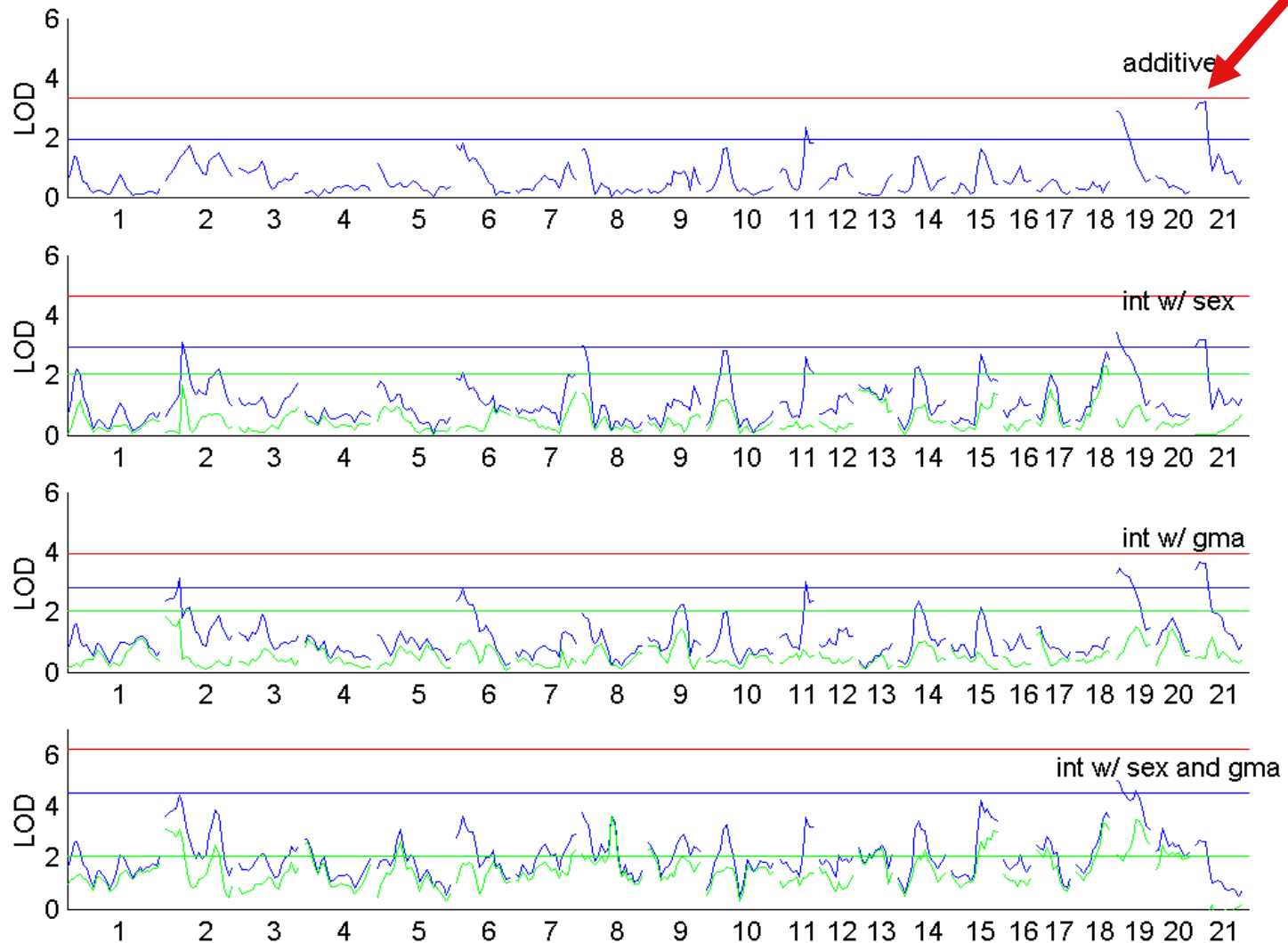
Correlation between phenotype (diagnosis) and genotype

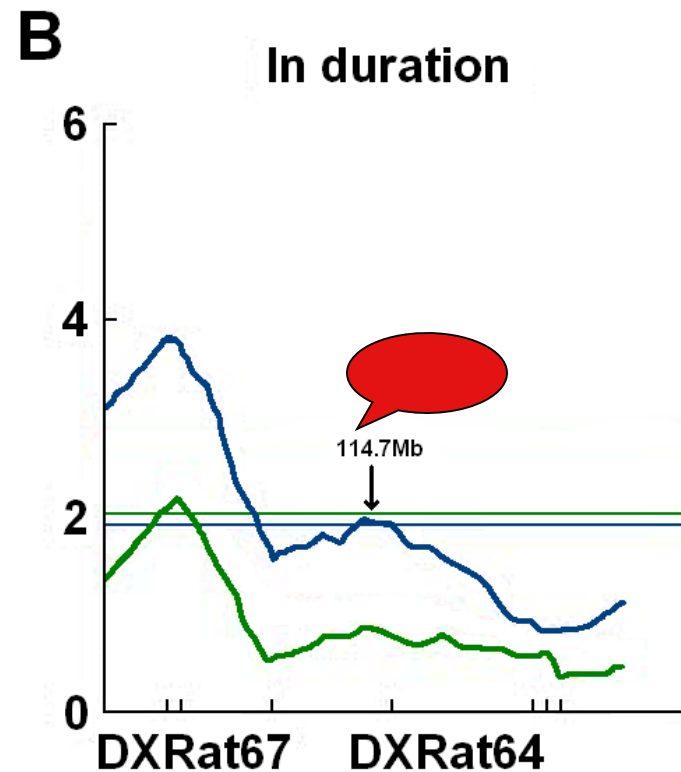
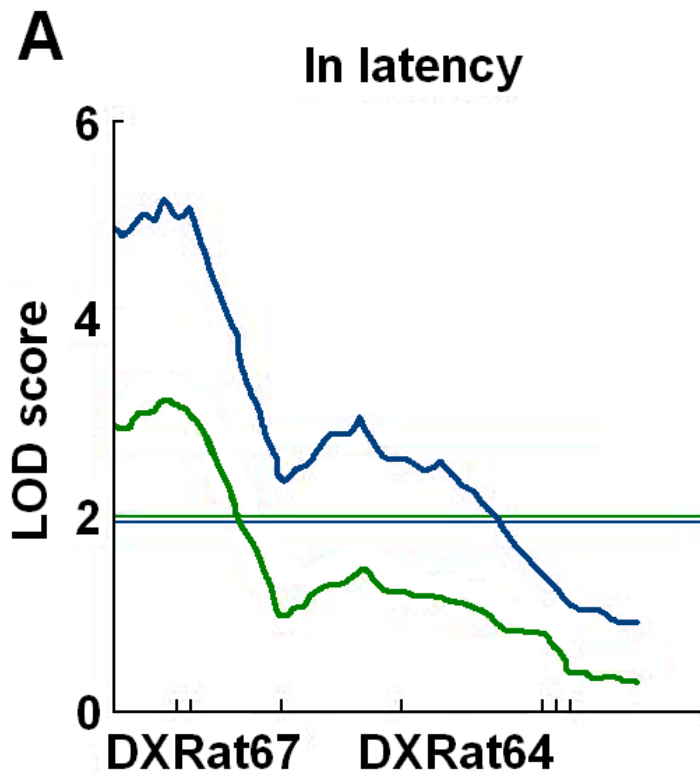
LUCK, LUCK, LUCK

Quantitative Trait Locus Analysis



Genome scan for duration of burying





Blue: unadjusted,
no covariates

$$(1) y = b_0 + b_1q$$

$$(2) y = b_0$$

Green: sex and lineage
as additive covariates

$$(3) y = b_0 + b_1x + b_2q$$

$$(4) y = b_0 + b_1x$$

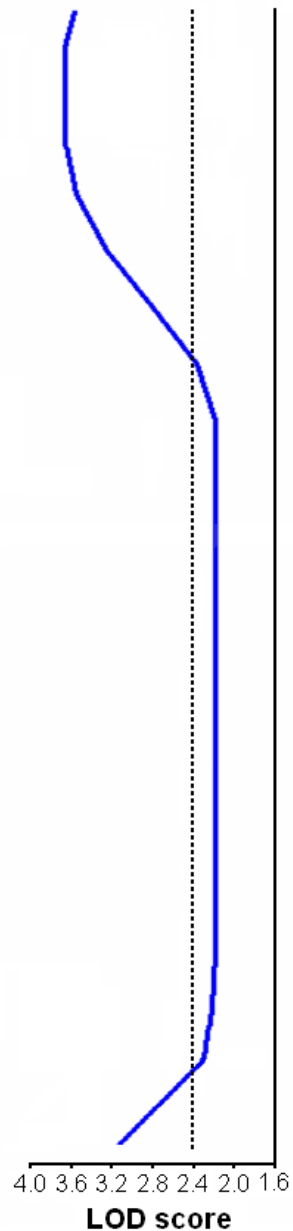
How is it done?

DNA: Mapping 500K Array Set

***RNA: The Human Genome U133 set
contains
transcripts derived from ~ 33,000 genes.***



— Duration LOD Score
 Significance Threshold



Genotype	Marker or SNP	Location (Mb)
F344		88,514,169
?		
?		
WKY	G/T	95,074,160
WKY	A/G	95,487,735
WKY	C/T	96,012,286
WKY	C/T	96,457,403
WKY	C/T	96,722,166
WKY	A/T	98,285,593
WKY	A/C	98,998,455
WKY	DxRat50	99,773,357
WKY	A/C	100,781,233
WKY	G/T	103,022,500
WKY	C/T	104,799,115
WKY	A/T	106,125,462
WKY	A/G	106,474,065
WKY	C/T	107,012,927
WKY	C/T	107,227,193
WKY	A/G	107,956,175
WKY	C/T	108,613,039
WKY	DxRat71	109,514,212
WKY	A/G	110,819,544
WKY	G/T	111,531,390
WKY	A/G	112,109,283
WKY	DxRat17	112,204,504
WKY	C/T	112,483,874
WKY	A/G	114,036,787
WKY	A/G	115,067,688
WKY	A/G	115,467,035
WKY	G/T	116,110,562
WKY	A/T	116,944,293
WKY	DxRat94	120,688,640
WKY	DxRat96	122,069,838
?		
F344		124,590,225

Candidate
Locations

← 1 - 4

← 5

← 6

← 7

← 8

← 9 - 13

← 14

Candidate	Brain Region	Fold Change
1.	Amygdala	-1.53
	Frontal Cortex	-1.42
	Hippocampus	-1.51
2.	Amygdala	-1.46
	Hippocampus	-1.56
3.	Amygdala	-1.20
	Hippocampus	-1.24
4.	Frontal Cortex	-1.19
	Hippocampus	-1.23
5.	Amygdala	-1.36
6.	Hippocampus	1.34
7.	Amygdala	-1.32
8.	Hippocampus	1.15
9.	Hippocampus	-1.22
10.	Hippocampus	-1.21
11.	Frontal Cortex	-1.16
12.	Frontal Cortex	1.11
13.	Frontal Cortex	1.12
14.	Amygdala	-1.34
	Hippocampus	-1.51

■ F344 Genotype
 □ Marker/SNP = BN ≠ F344
 ■ Marker/SNP ≠ BN ≠ F344
 ■ Region with no Markers/SNP

Biomarker candidates for human depression

