

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

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# Animal models

## **Behavior**

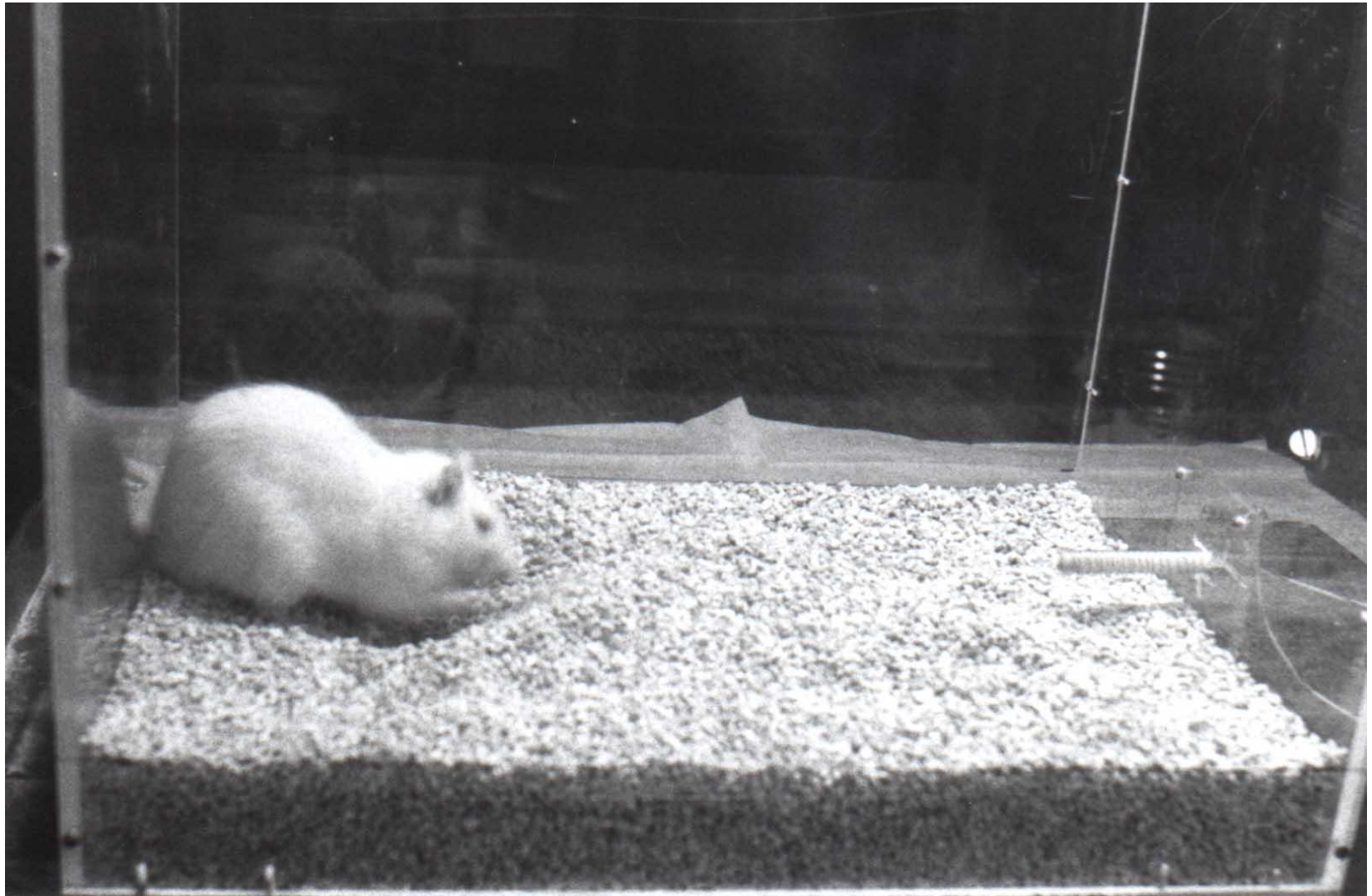
- Defensive Burying
- Elevated Plus Maze
- Light-Dark Box
- Social interaction
- Forced Swim Test
- Morris Water Maze
- Object recognition

## **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

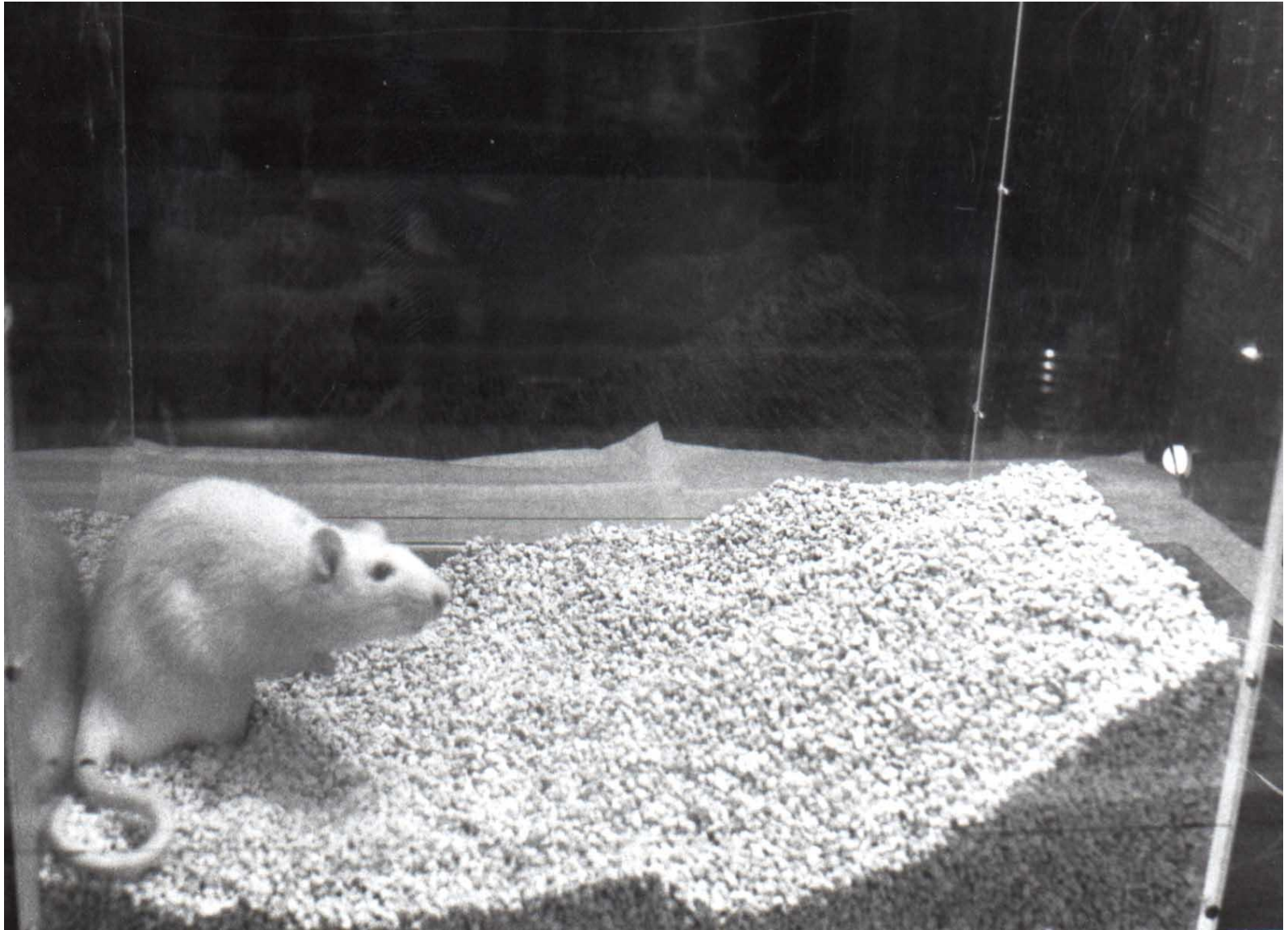
- Forced Swim Test
  - Learned Helplessness
  - Open Field Test
  - Elevated Plus Maze
  - Defensive Burying
  - Light/Dark box
  - Open field Arena
- ↑ immobility  
escape behavior  
↓ exploration  
↓ decision  
↓ passive coping  
↑ ambivalence  
↑ feeding  
↓



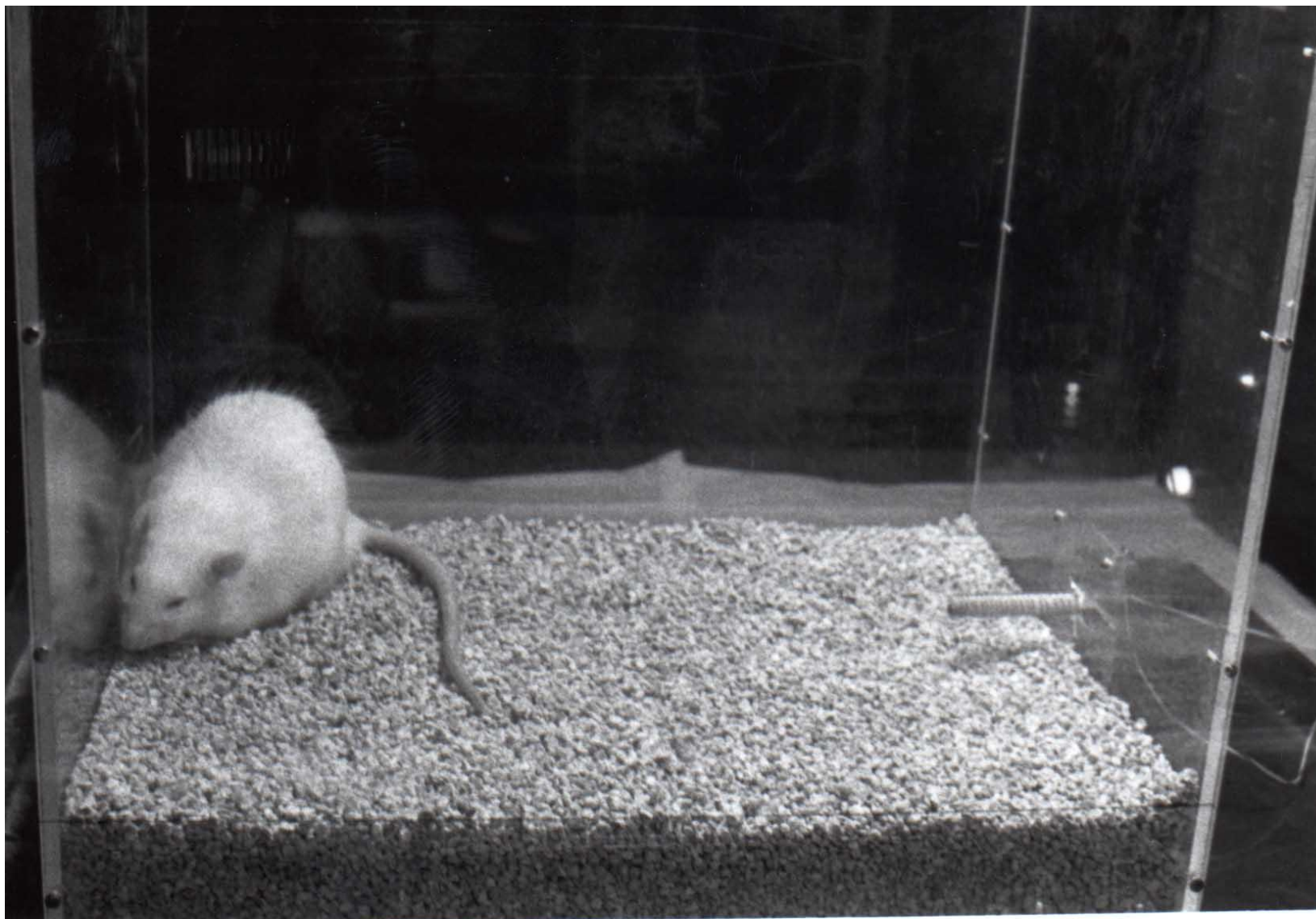
Neuroendocrinology Symposium,  
Istanbul, 2009



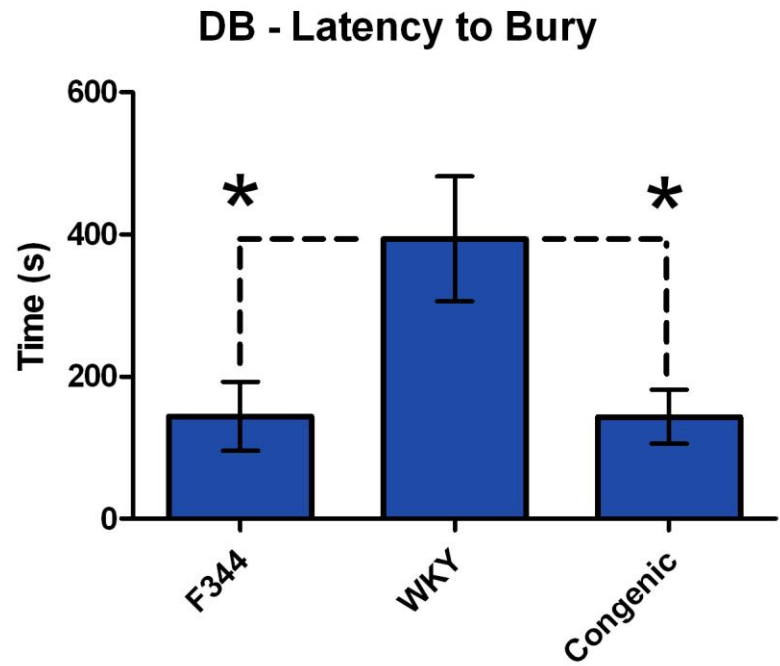
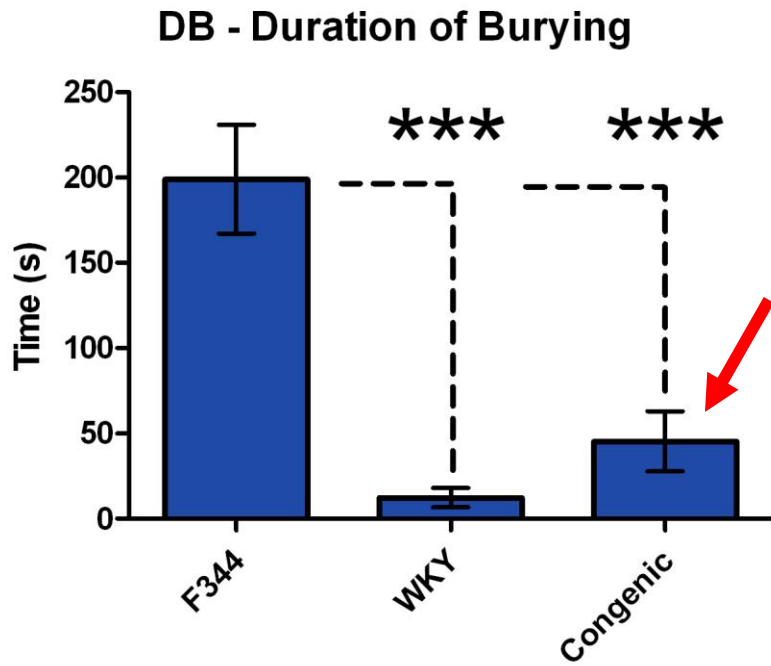
Neuroendocrinology Symposium,  
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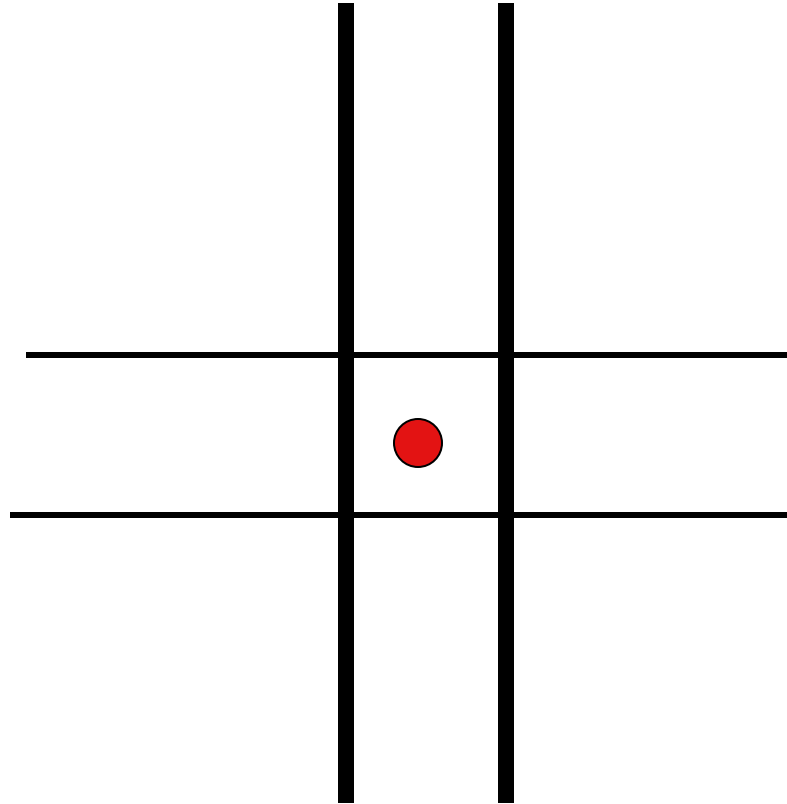
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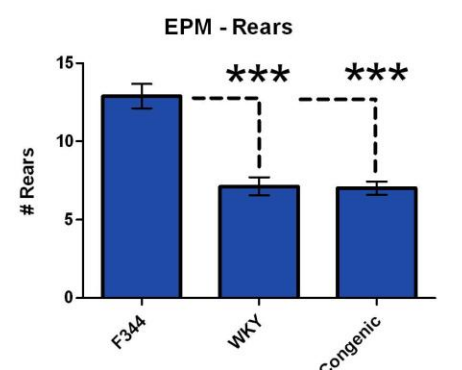
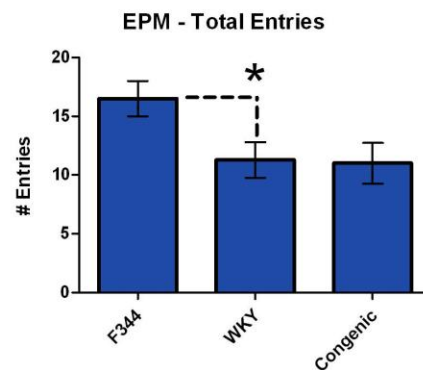
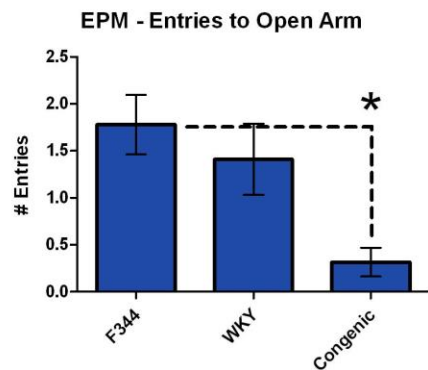
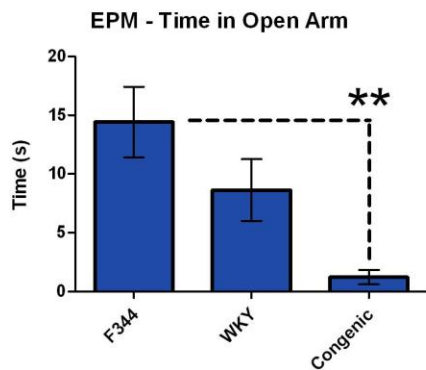
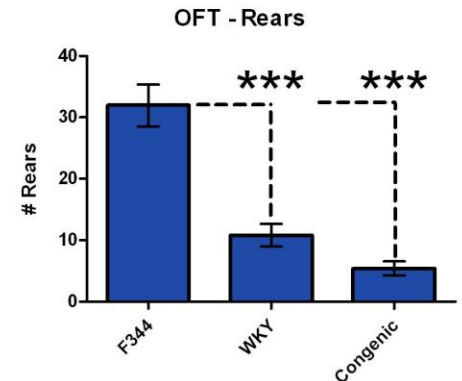
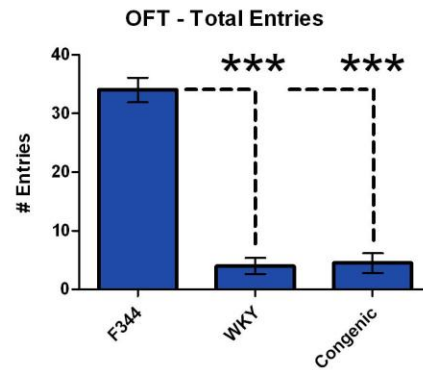
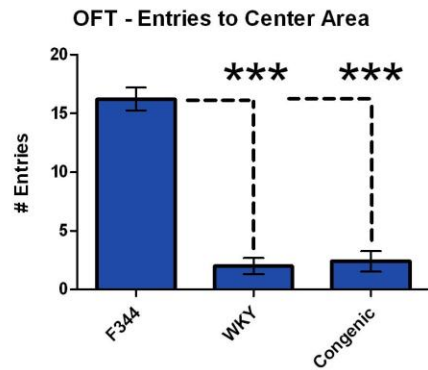
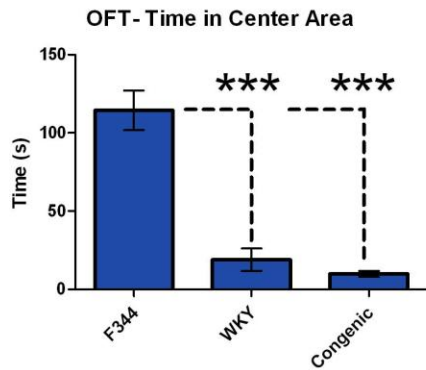
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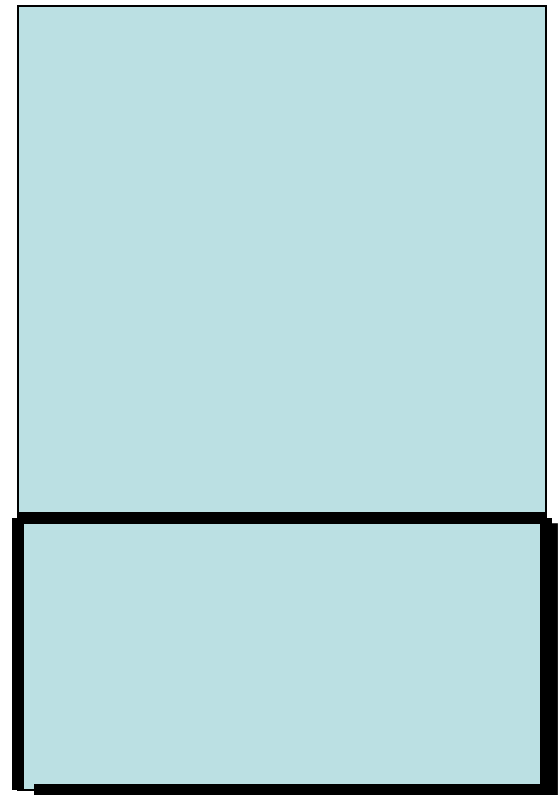
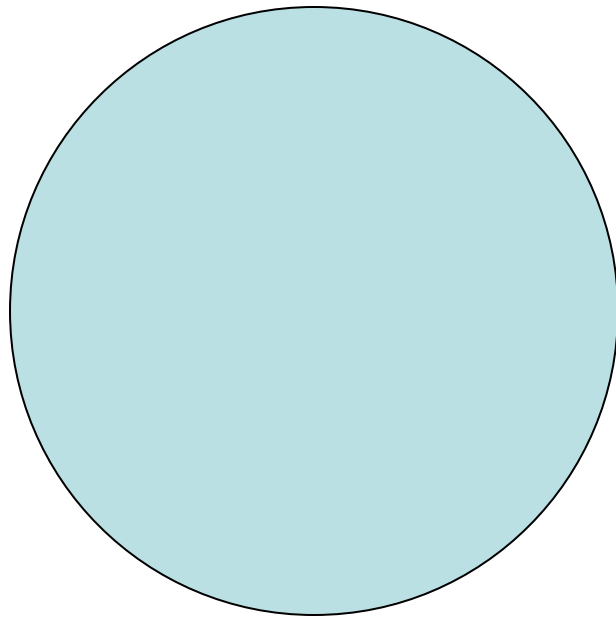
# Elevated Plus Maze



Neuroendocrinology Symposium,  
Istanbul, 2009



# 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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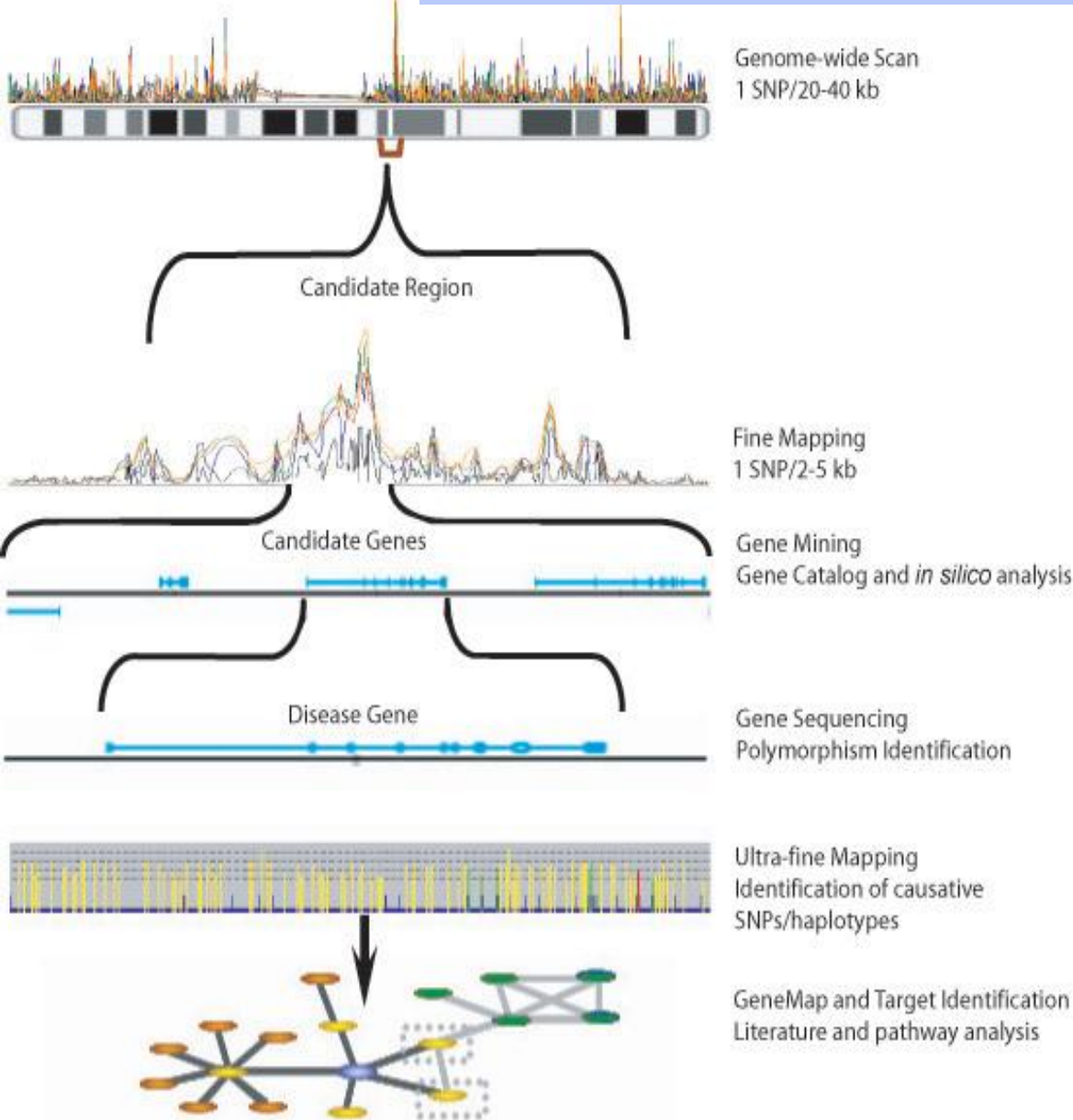
## **Genetics, transcriptomics**

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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



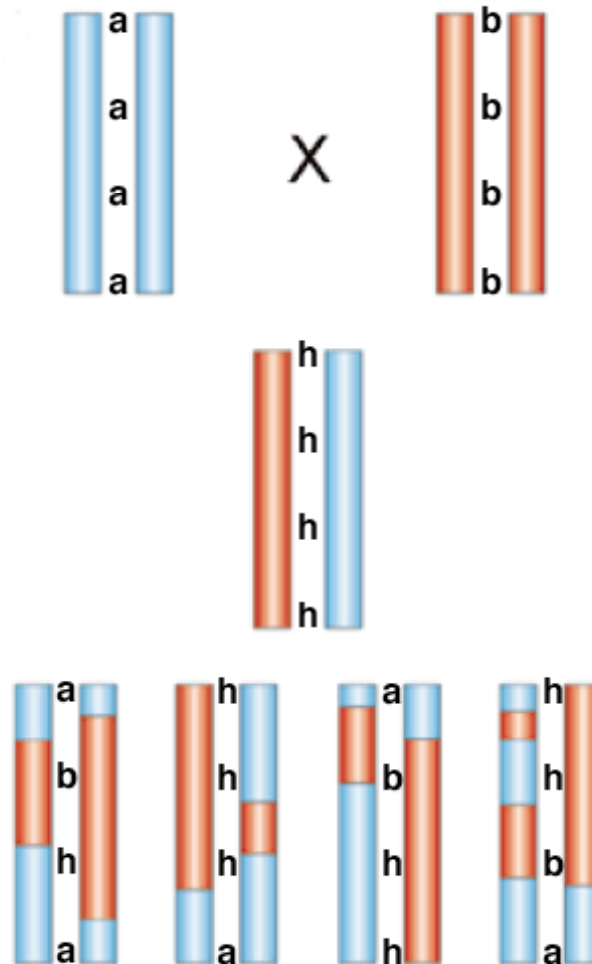
*DNA samples from a large population that is properly diagnosed. Without an easy laboratory test it is **HARD**.*

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

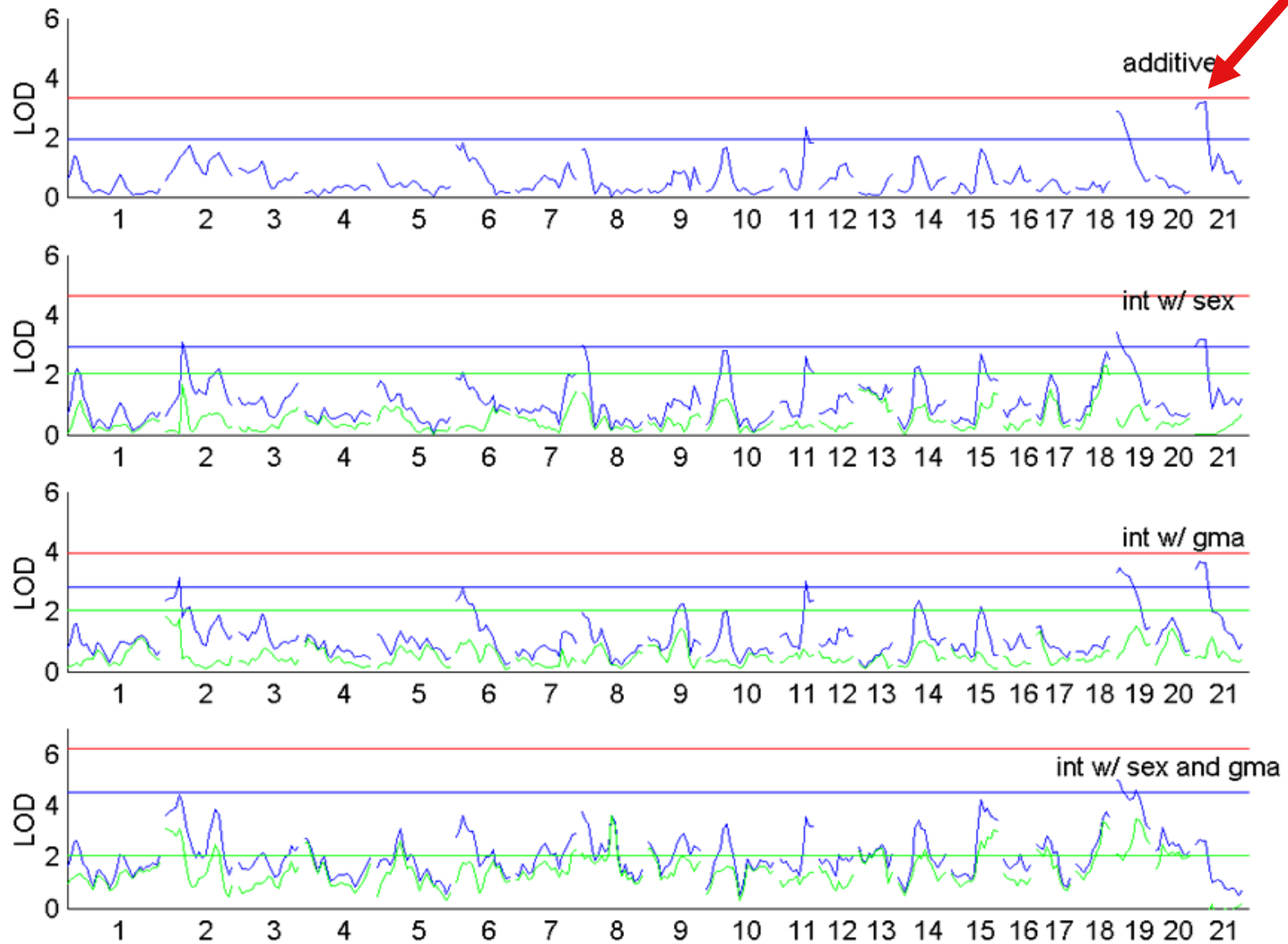
*Correlation between phenotype (diagnosis) and genotype*

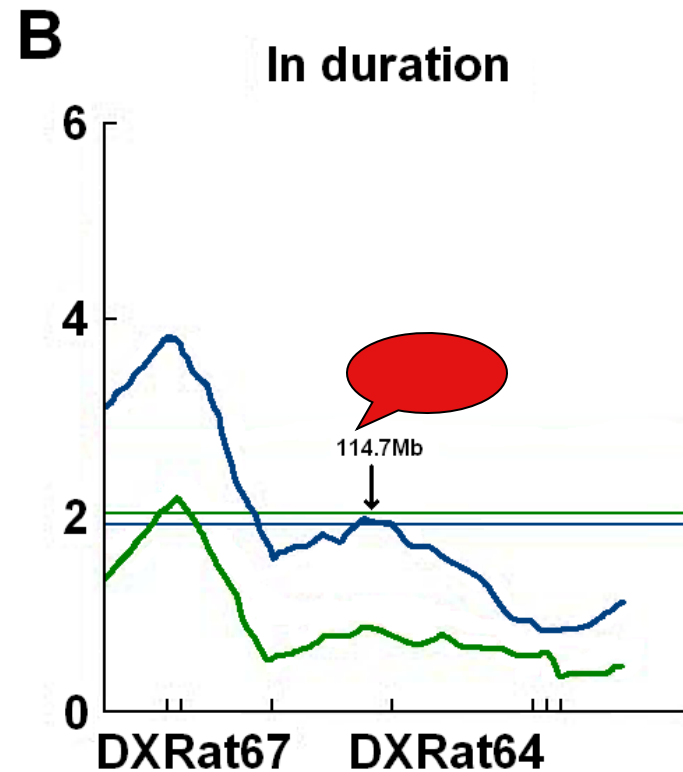
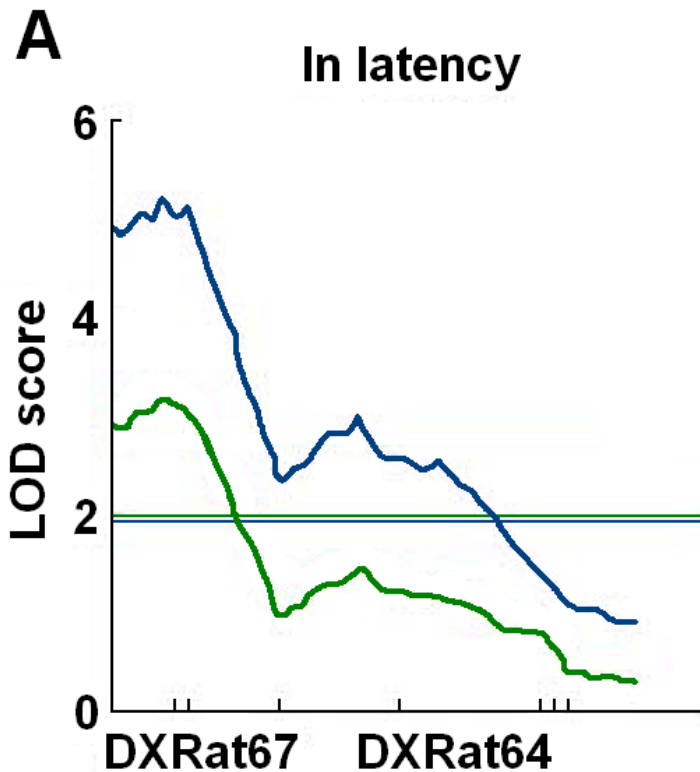
***LUCK, LUCK, LUCK***

# Quantitative Trait Locus Analysis



# Genome scan for duration of burying





Blue: unadjusted, no covariates	Green: sex and lineage as additive covariates
(1) $y = b_0 + b_1q$	(3) $y = b_0 + b_1x + b_2q$
(2) $y = b_0$	(4) $y = b_0 + b_1x$

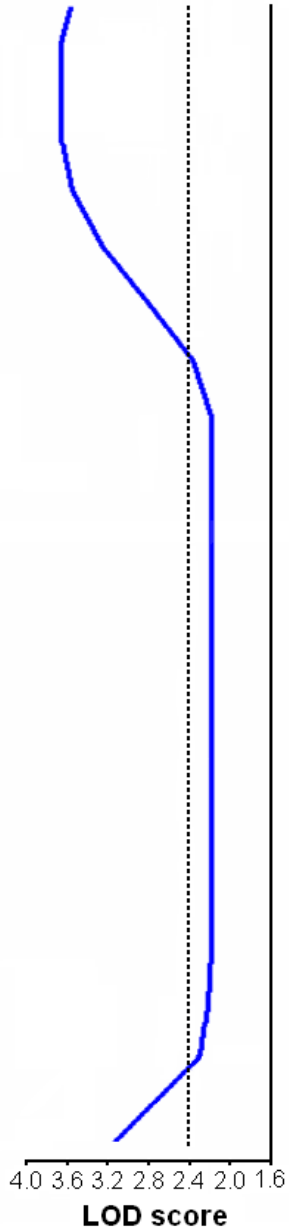
## *How is it done?*

***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

