

# Biomarkers for Depression

Husseini K Manji, MD

*Director, Mood & Anxiety Disorders Program*

*National Institute of Mental Health*

*National Institutes of Health*

*US Dept of Health and Human Services*



# Biomarkers in Depression

Major Questions: UP vs BP? (major treatment considerations)  
Identification of at-risk individuals; ? Prodromal  
Rx Response

## 1. CNS markers

1. CSF chemical measures -- proteomics, metabolomics
2. Regional morphometric measures -- left subgenual anterior cingulate volume
3. *in vivo* functional neuroimaging measures -- PET -- Area 25 Activity
4. Provocative *in vivo* neuroimaging measures (task and chemical induced changes)
  - fMRI Amygdala activation
  - Reward Circuitry metabolism in response to AMPT
  - (? Rebound hypomania to AMPT useful to distinguish UP/BP)?

## 2. Peripheral markers

1. Plasma or serum chemical measures -- proteomics, metabolomics promising
2. Peripheral, accessible tissue -- transcriptomics, & intracellular signaling

## 3. Physiological markers

MEG, high density EEG to study *in vivo* regional plasticity

\*\*\*\* Pharmacogenomics to predict therapeutic response & side effects

# Pharmacogenomics of Antidepressant response

- § **Antidepressants are effective in ~50% of patients; current Rx is “trial & error” (with weeks-long trials)**
  
- § **Individual variation in outcome may have a partial genetic basis**
  - **outcome and side-effect patterns vary less between illness episodes than between individuals**
  - **outcome of treatment may run in families**
  
- § **Approach -- Study a large group of people who were all treated with the same medication and followed longitudinally**
  - **STAR\*D Cohort: 1953 people, all with major depression (“real world patients”), all treated initially with an SSRI, citalopram (12 weeks @ level 1). 1 yr f/u**
  
- **Test for association between outcomes (response, side effects) and genotypes**

# Pharmacogenomic Study Strategy

- Genes selected and scored by expert panel
- **68 Genes sampled by first 768 SNPs selected for inclusion in Phase 1 screen**
- Sampled with SNPs selected from HapMap Phase 1 at  $r^2 \leq 0.80$
- **Performed at Illumina, Inc. using BeadArray and GoldenGate assay**
- 99.78% of samples were successfully genotyped
- **97.92% of SNPs produced usable data**
- 100% agreement among 11,280 blind duplicates
- **Additional SNPs near positive association signals genotyped at NIMH Lab using Taqman; 100% agreement between Illumina data and Taqman data based on blind duplicates**

# Analysis Plan

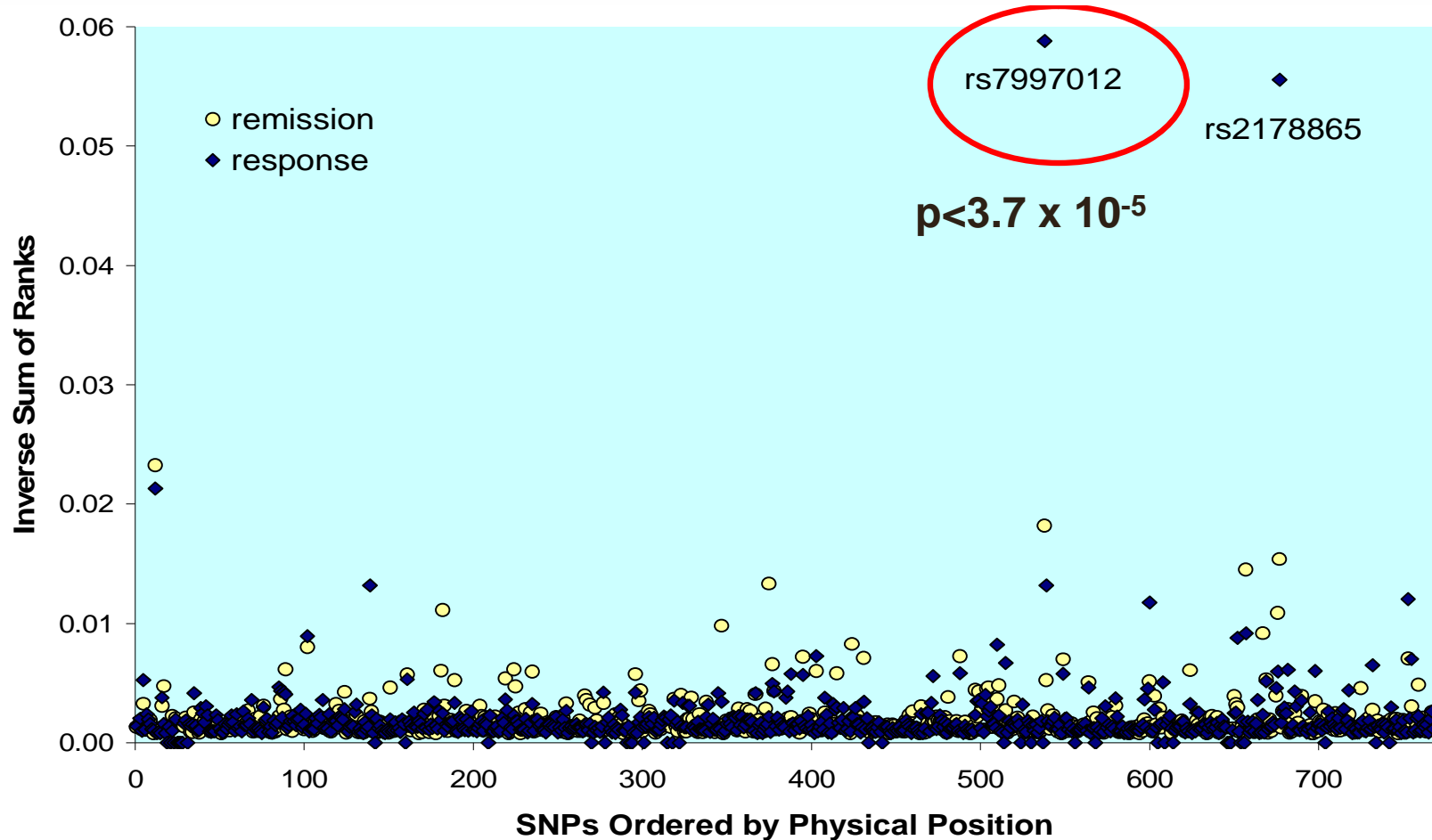
- Split sample design: 2/3 test and 1/3 replication
  - Split samples matched on gender and self-reported race
- **All SNPs screened by allelic and genotypic tests**
- Based on power analysis, alpha was set at 0.01 for the test sample and 0.05 for the replication sample
- **Pass criteria: same allele, same test, same phenotype**

Outcome phenotype:

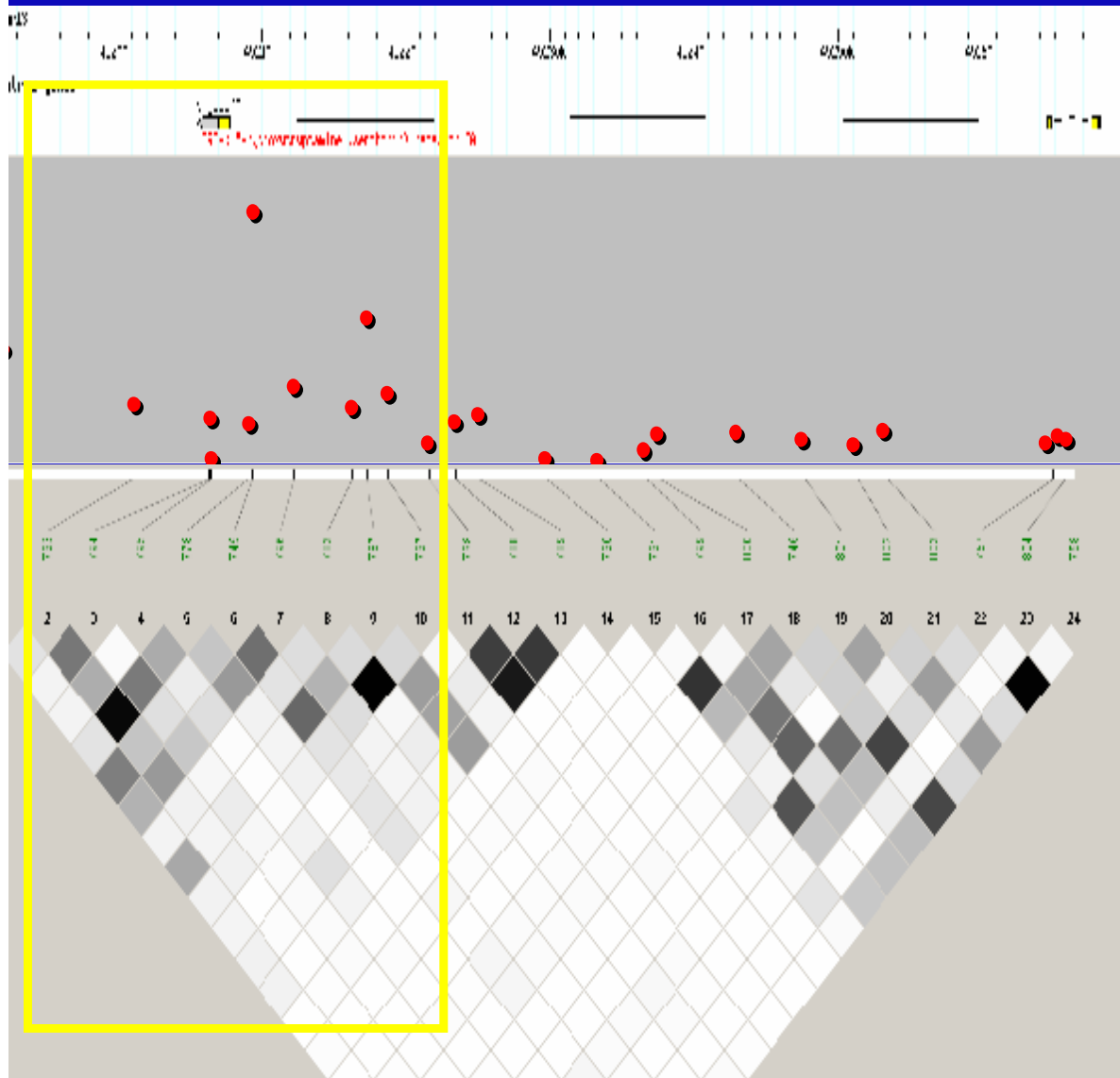
- **Remitters:** score of  $\leq 5$  at the last visit on the QIDS-C
- **Responders:** at least a 50% reduction from baseline on the QIDS-C

# Variation in the Gene Encoding the Serotonin 2A Receptor Is Associated with Outcome of Antidepressant Treatment

Francis J. McMahon,<sup>1,\*</sup> Silvia Buervenich,<sup>1,\*</sup> Dennis Charney,<sup>3</sup> Robert Lipsky,<sup>4</sup> A. John Rush,<sup>5</sup> Alexander F. Wilson,<sup>6</sup> Alexa J. M. Sorant,<sup>6</sup> George J. Papanicolaou,<sup>6</sup> Gonzalo Laje,<sup>1</sup> Maurizio Fava,<sup>7</sup> Madhukar H. Trivedi,<sup>5</sup> Stephen R. Wisniewski,<sup>8</sup> and Husseini Manji<sup>2</sup>

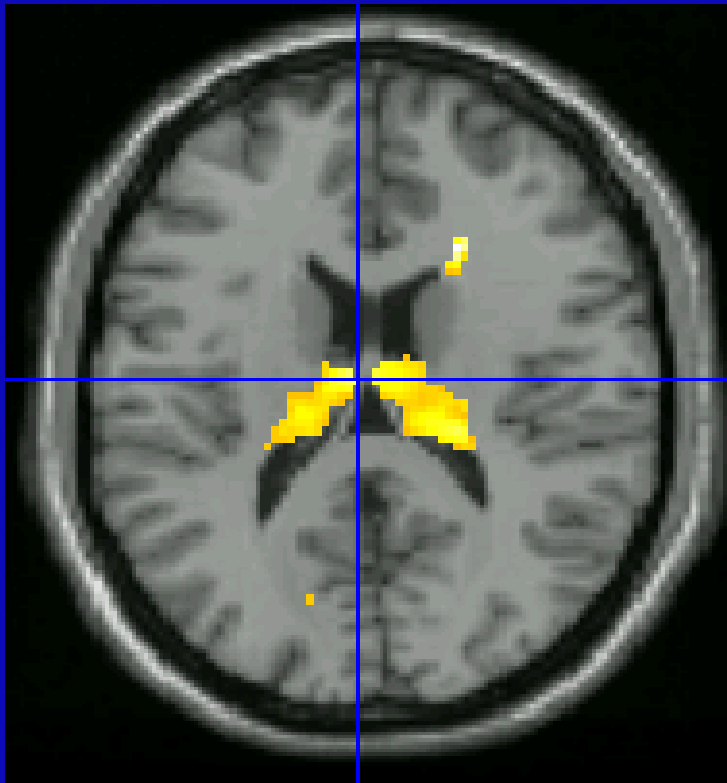


# Secondary Screen of HTR2A Response Phenotype (whites)

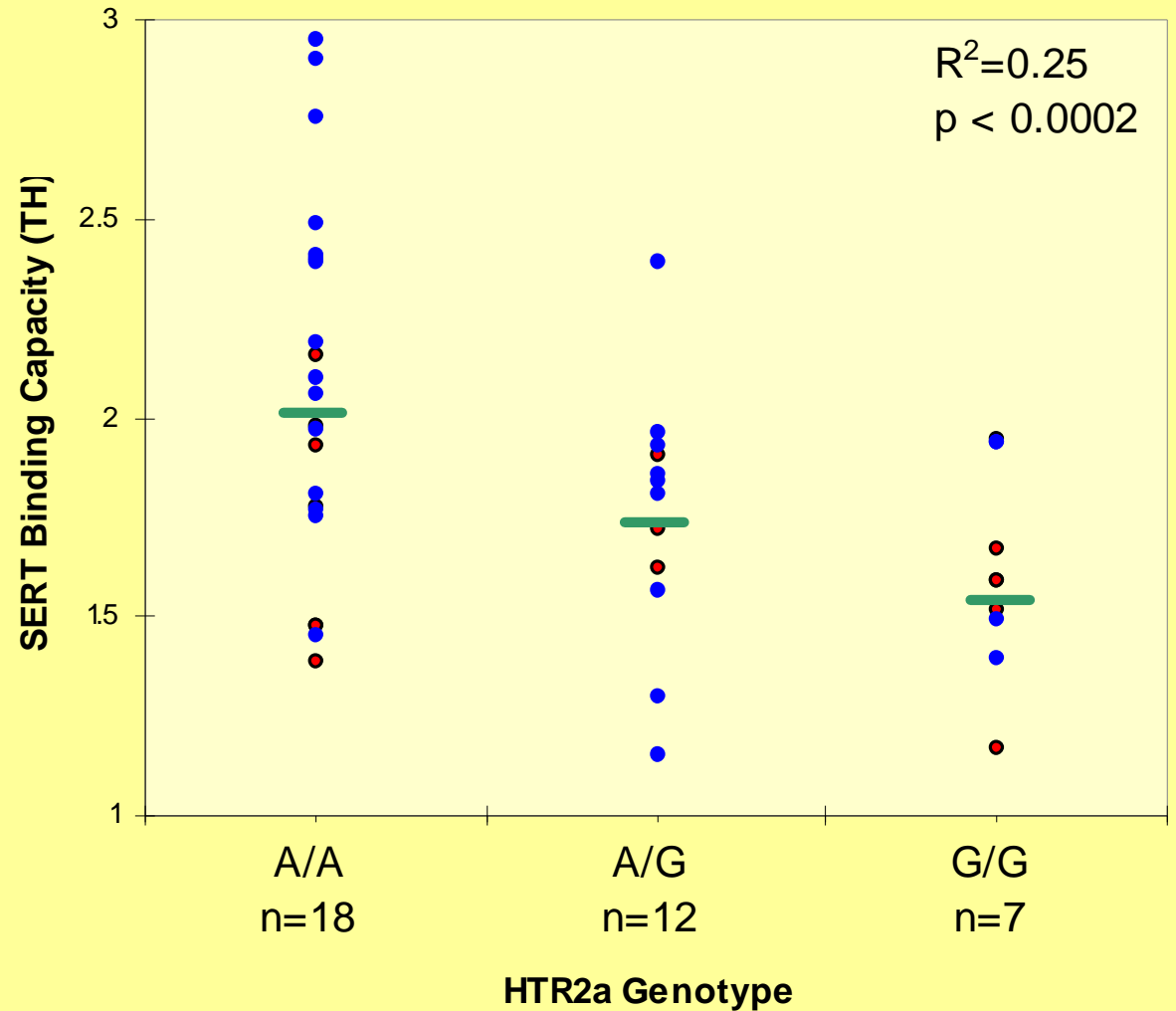


- The allele associated with better outcome was ~7 times more common in whites than blacks
- Blacks also had a less favorable outcome, overall, than whites in this sample

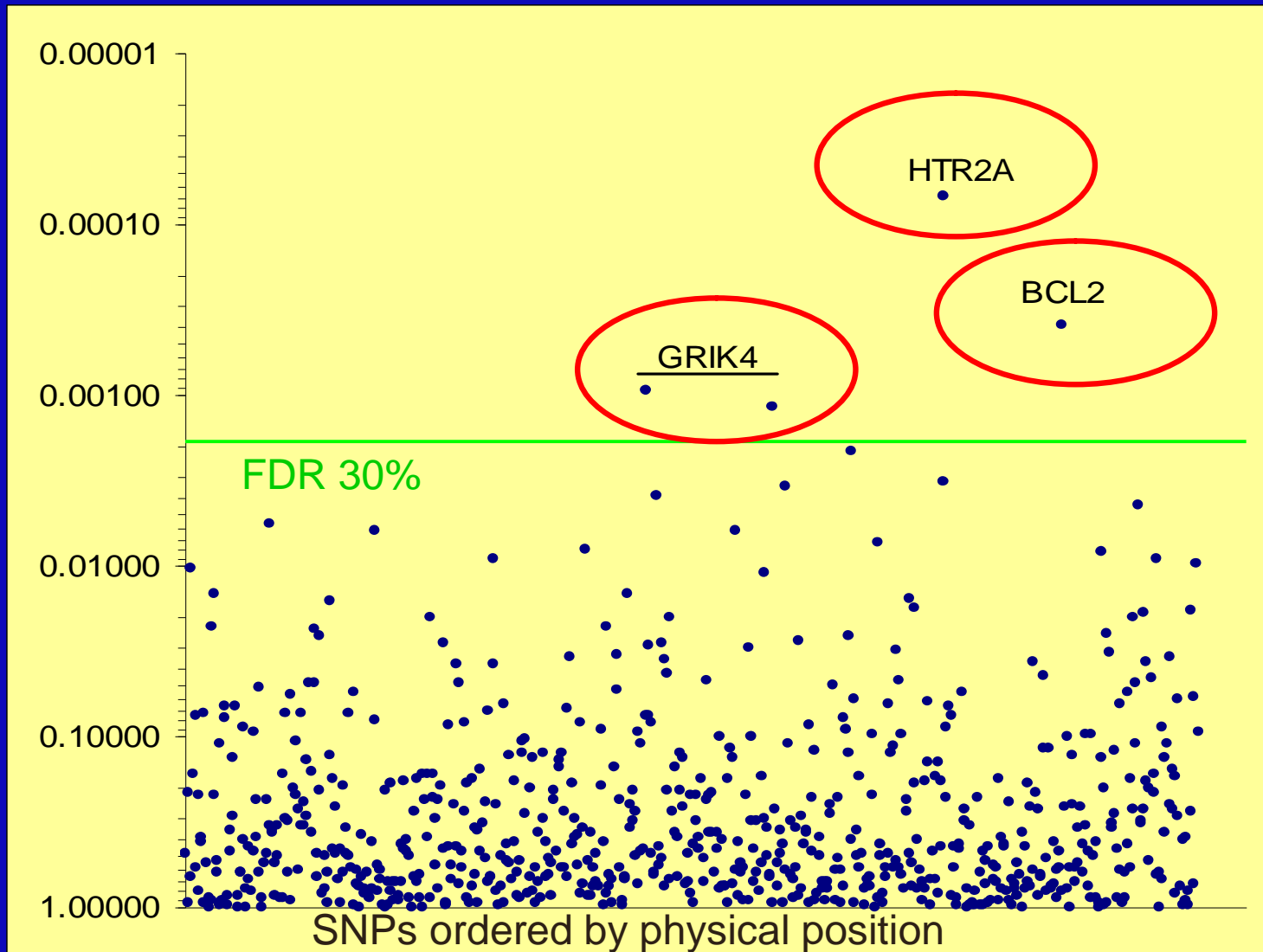
# The allele associated with better outcome is also associated with greater SERT binding capacity



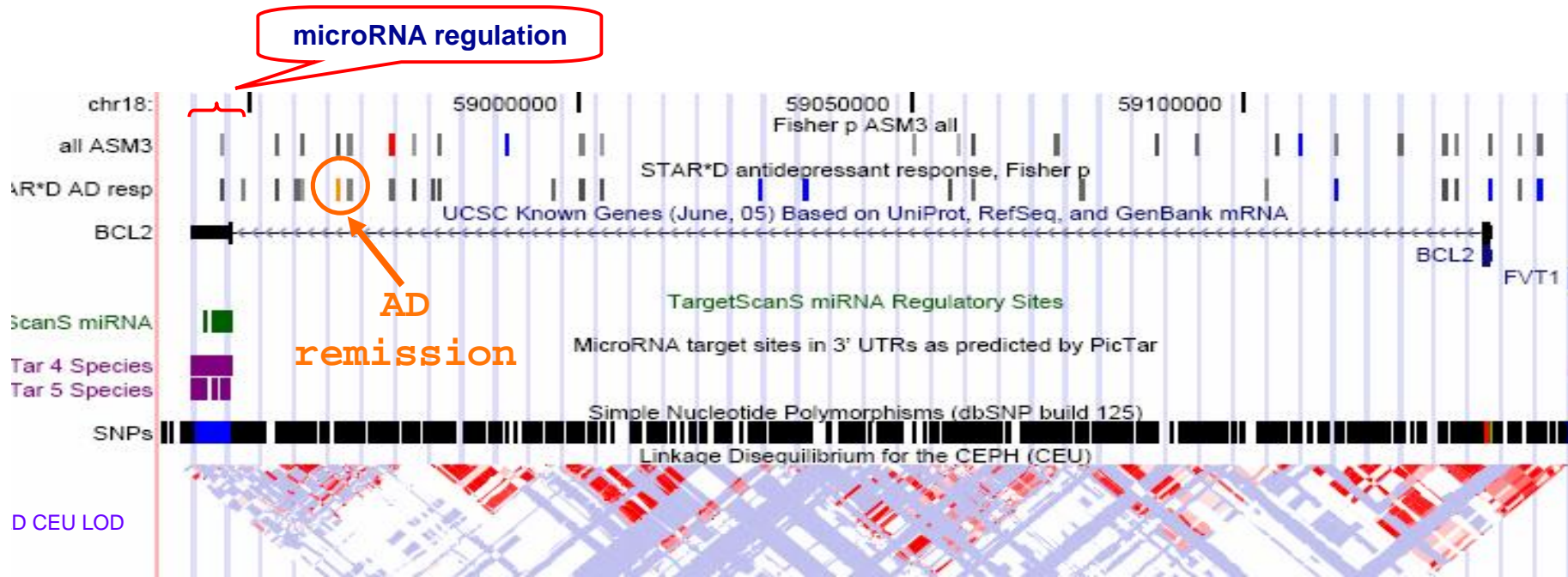
T-map showing [11C]DASB Binding



# Other Genes associated with Treatment Response

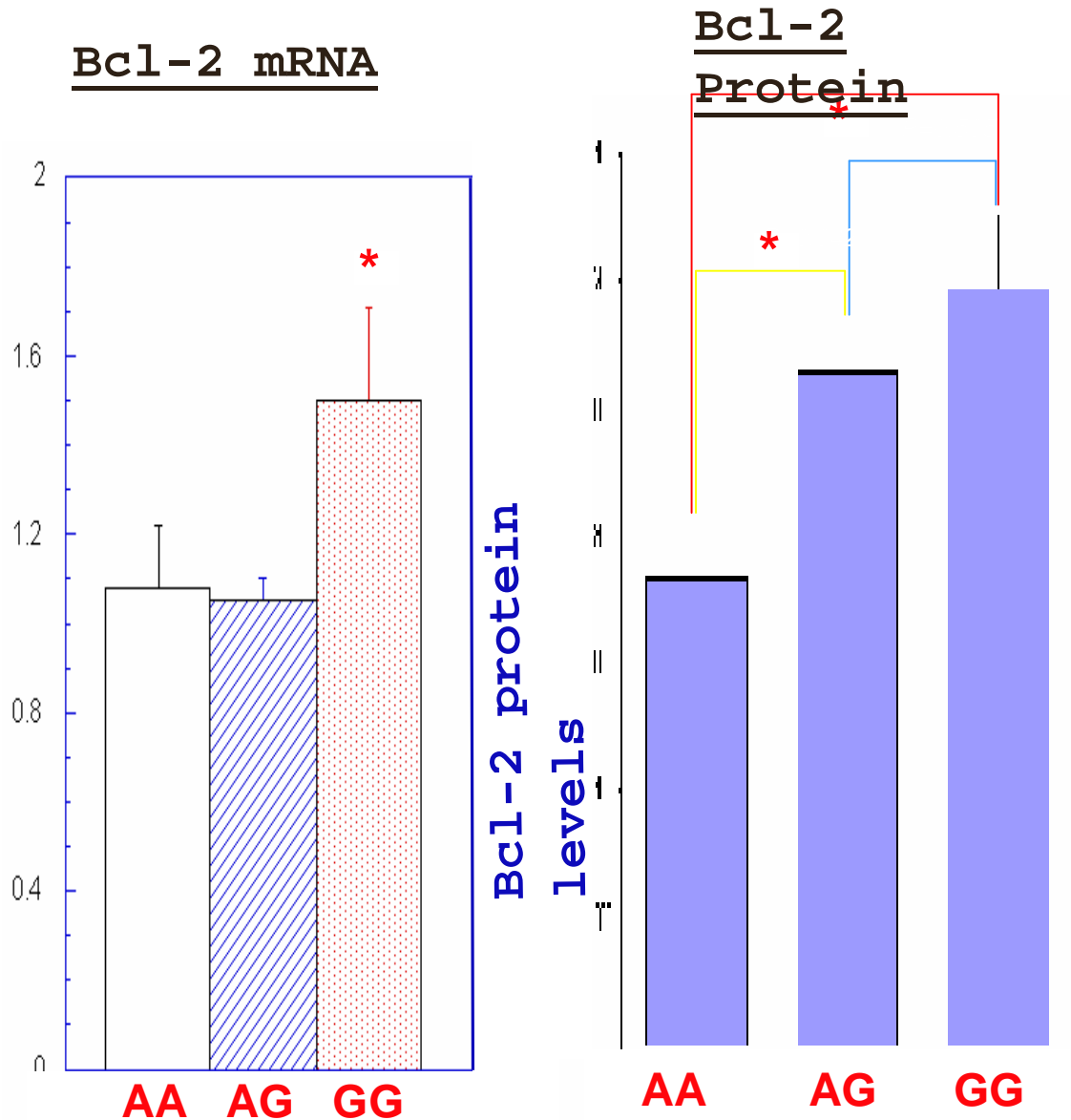


# Bcl-2 represents a gene conferring responsivity to antidepressants

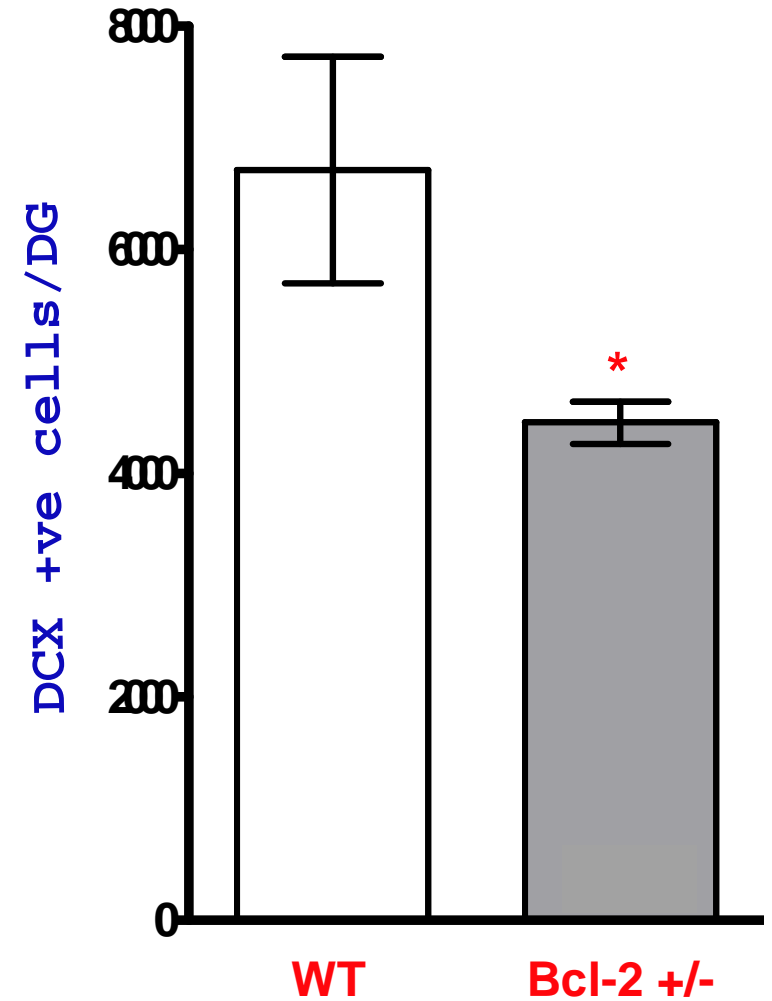


Participants homozygous for the response-associated allele were 40% more likely to go into full remission after 6 weeks of citalopram

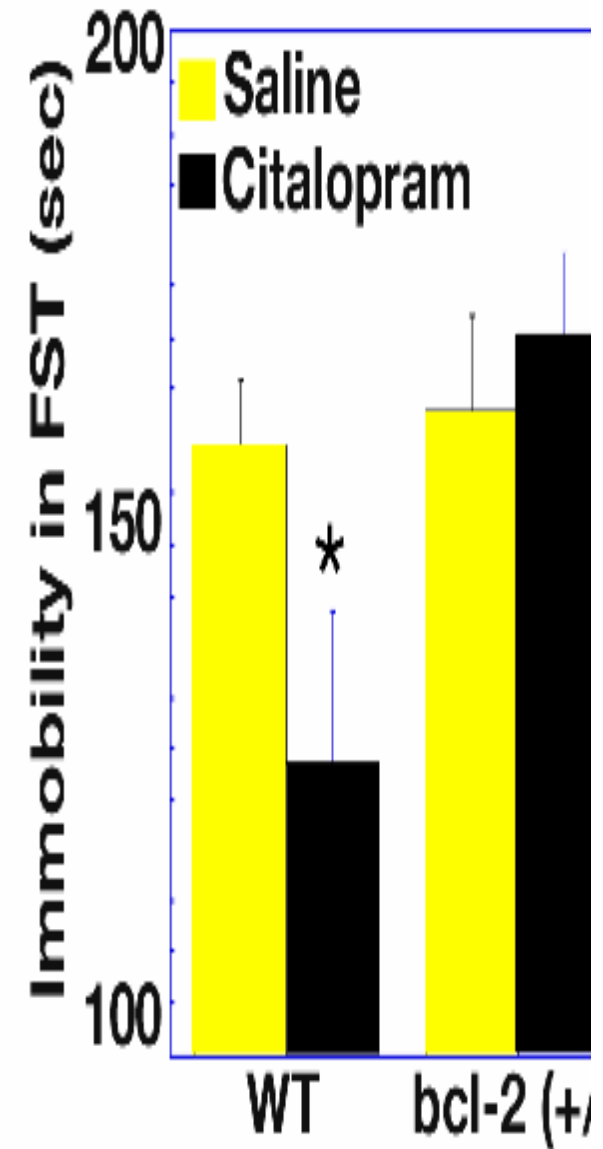
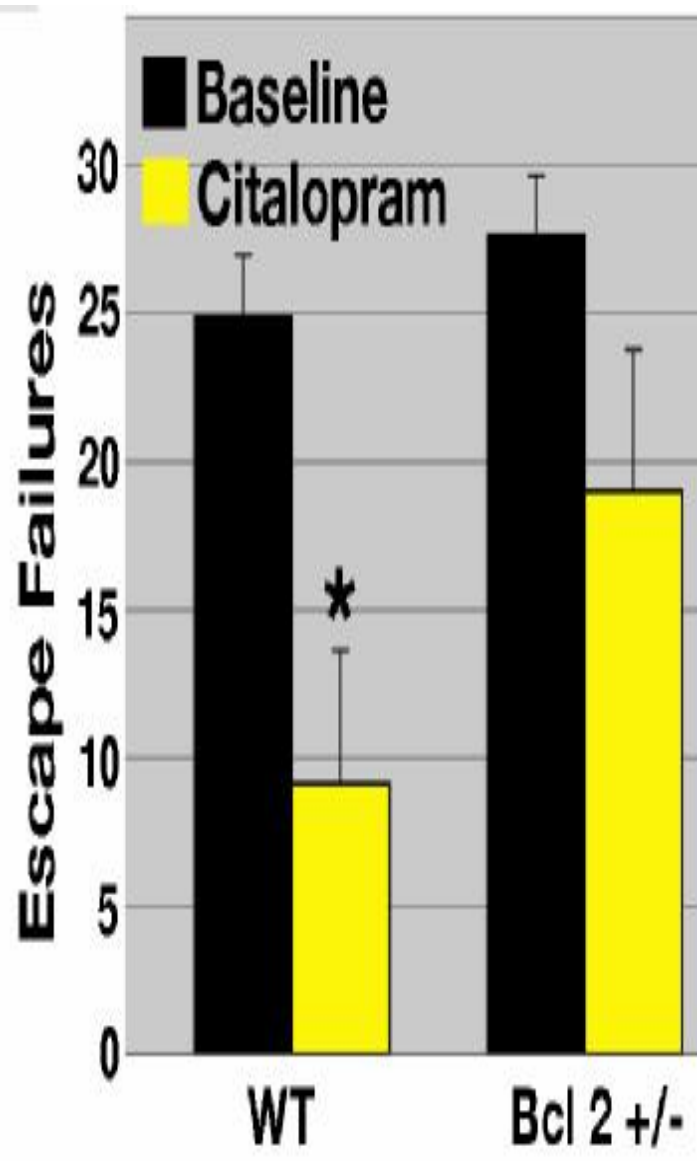
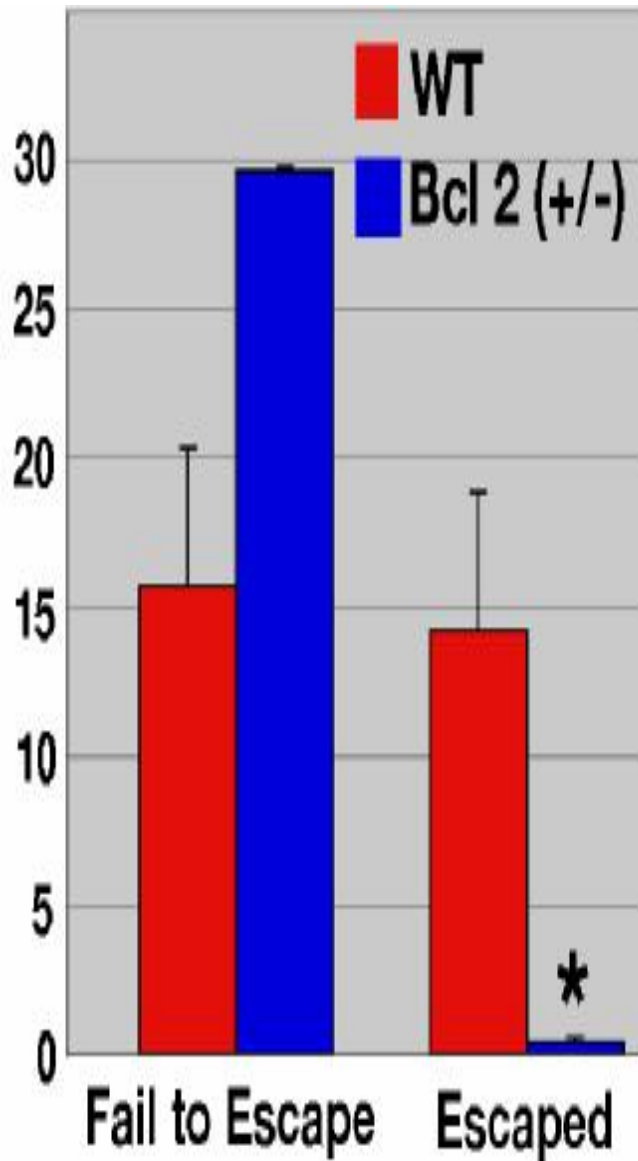
Bcl-2 SNPS regulate Bcl-2 mRNA, protein levels & sensitivity to apoptosis



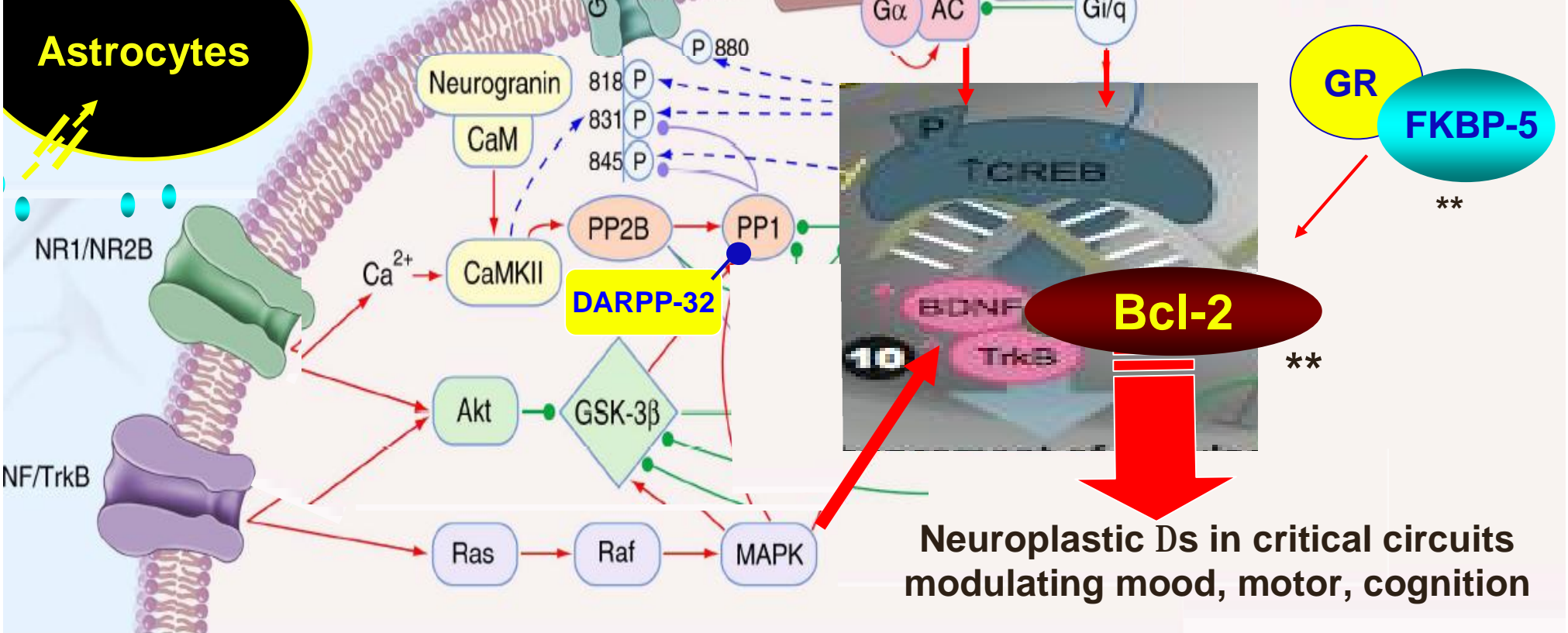
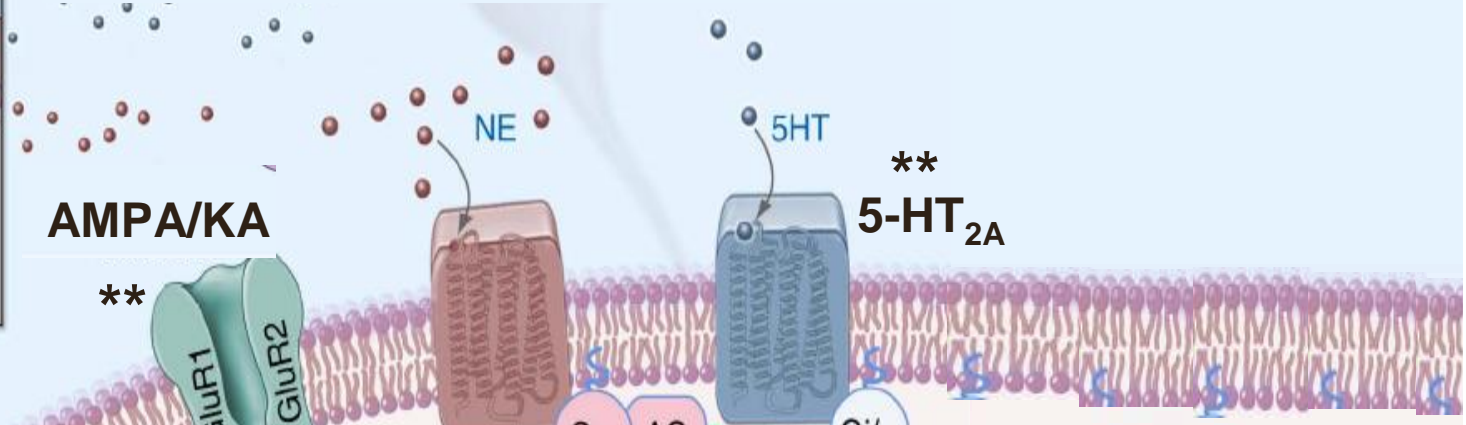
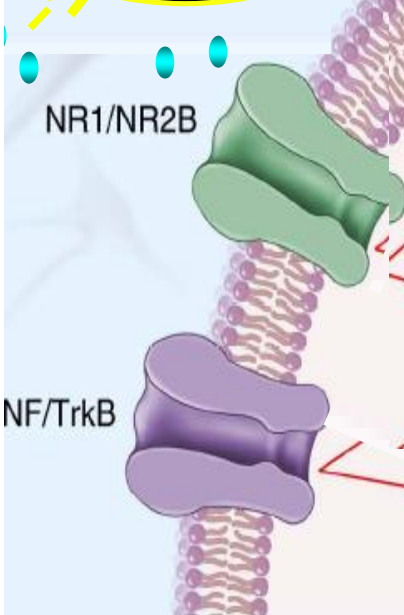
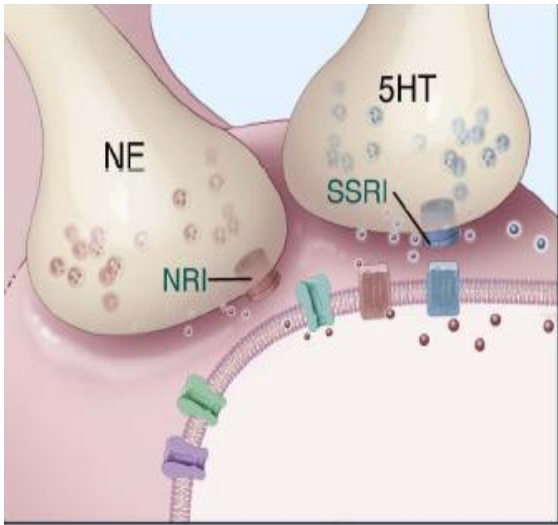
Bcl-2 +/- mice show reduced DG neuroblasts (doublecortin)



**Bcl-2 +/- mice develop learned helplessness at a markedly greater rate, and fail to respond to citalopram**



# Genes Associated with Antidepressant Responsiveness

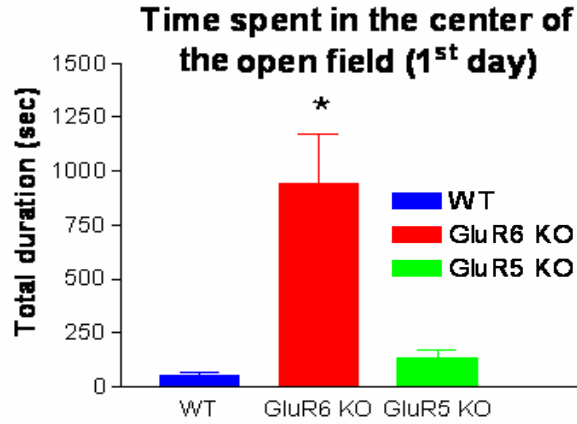
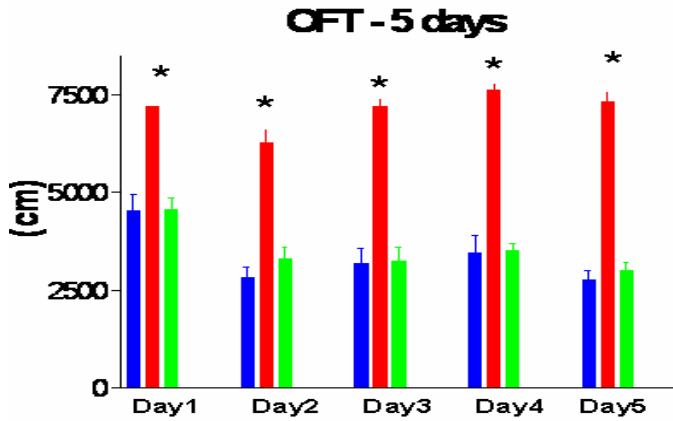


Neuroplastic Ds in critical circuits modulating mood, motor, cognition

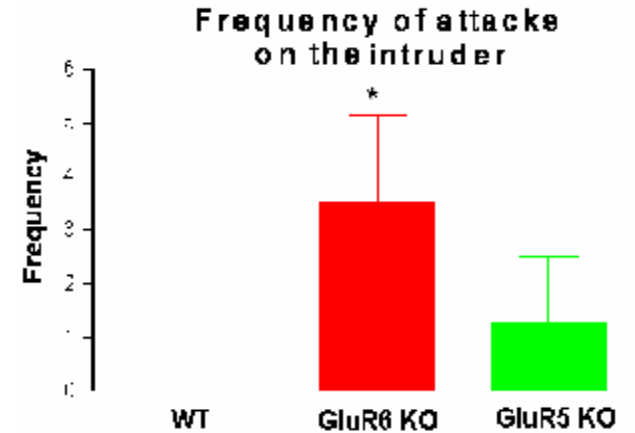
# GluR6 KO mice display hyperlocomotion, aggression and increased exploratory behaviors (all lithium responsive)

- Con
- GluR6 ko
- GluR5 ko

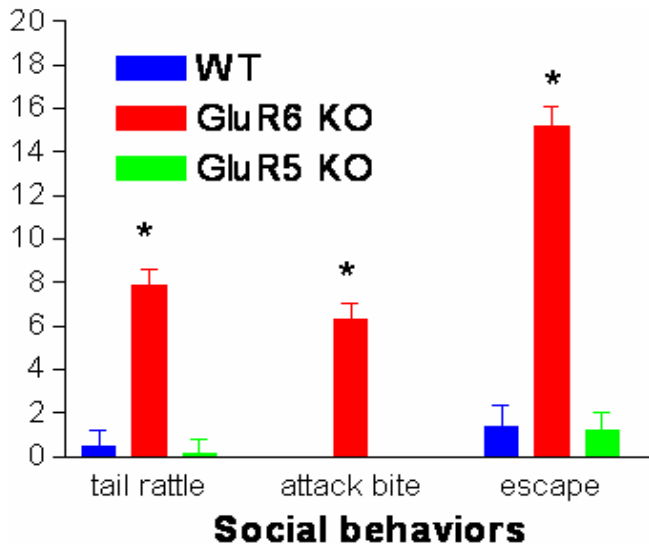
## Hyperactivity



## Aggression

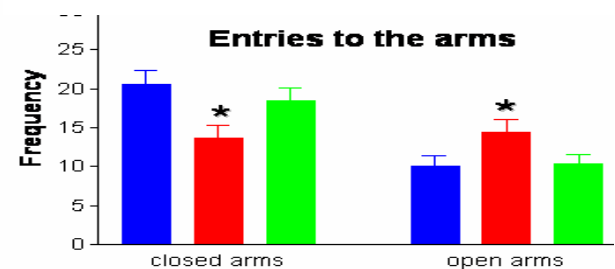
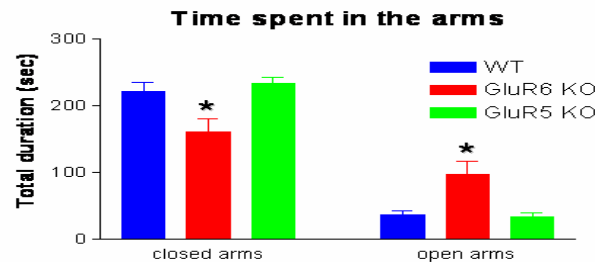
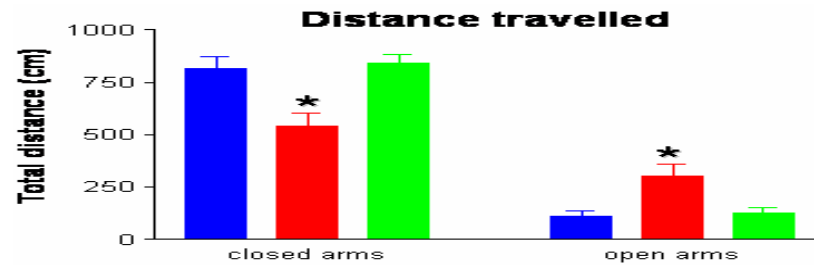


## Aggression



## “Risk taking”/Exploratory

N= 12 (WT),  
(GluR6 KO), 13  
(GluR5 KO)



# Conclusions

- Outcome of citalopram treatment is related to common variants in at least 3 genes (likely more)
- WGS Pharmacogenomic studies have the potential to play an important role in personalizing Rx for this heterogeneous (but devastating group of illnesses)

# Collaborators – STAR\*D Study

## **UT Southwestern – Dallas**

John Rush

Madhukar Trivedi

## **Mount Sinai School of Medicine**

Dennis Charney

## **University of Pittsburgh**

Stephen Wisniewski

## **Massachusetts General Hospital**

Maurizio Fava

## **NIMH**

Francis McMahon

Silvia Buervenich

Gonzalo Laje

## **NIAAA**

Robert Lipsky

## **NHGRI**

Alexander Wilson

Alexa Sorant

George Papanicolaou