# Identifying Genes in the Prefrontal Cortex Associated with Bipolar Disorder

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# Introduction

- Bipolar disorder is a mental disorder that causes extreme shifts in mood generally from periods of high energy and excitement (manic episodes) to periods of hopelessness, sadness, and low energy (depressive episodes).
- The prefrontal cortex is responsible for mediating complex cognitive behavior, personality expression, decision making, and moderating social behavior.
- The purpose of this project was to identify candidate genes associated with bipolar disorder by analyzing gene expression patterns located in the prefrontal cortex.

# Methods

Gene expression data for the Frontal Lobe was collected from the The Allen Brain Atlas (<a href="http://www.brain-map.org">http://www.brain-map.org</a>) using the differential search option. Data was collected from four available donors: H0351.1009, H0351.1012, H0351.2002, and H0351.2001.

Venny 2.1.0 (<a href="http://bioinfogp.cnb.csic.es/tools/venny/">http://bioinfogp.cnb.csic.es/tools/venny/</a>) was used to compare the gene lists from four chosen brain donors to identify genes that are common and different across each donor.

Statistical analysis was done in Python Anywhere (https://www.pythonanywhere.com) an online programming tool

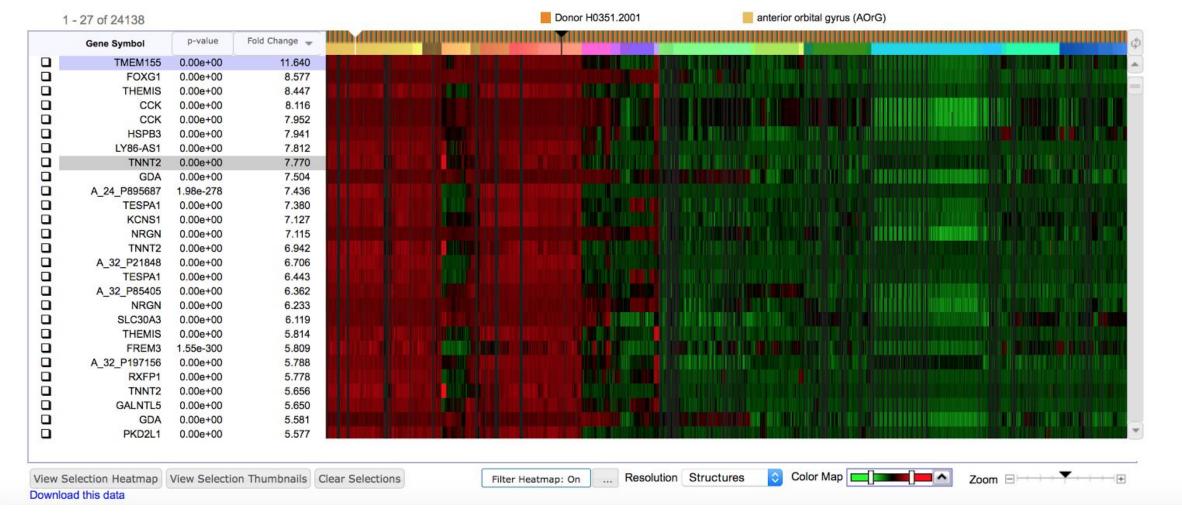
Cluster analysis and Gene Ontology classifications were obtained with DAVID (https://david.ncifcrf.gov)

The STRING database (<a href="http://string-db.org">http://string-db.org</a>) was used to identify potential interacting partners, pathways, and other genes relating to learning.

# Results

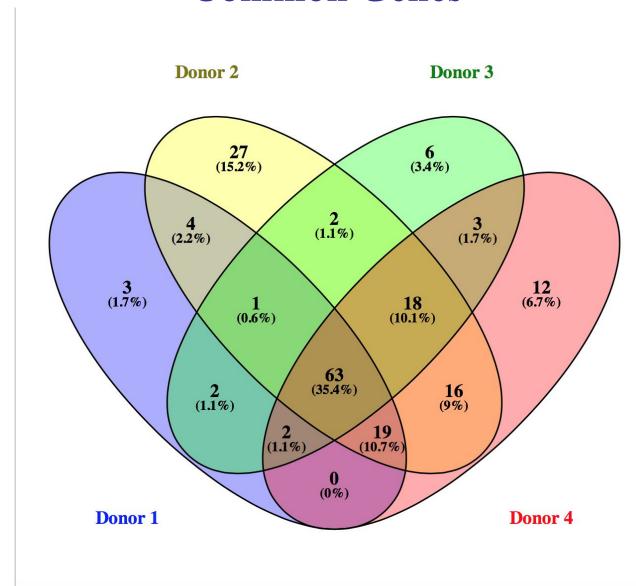
# **Gene Expression Profiling**





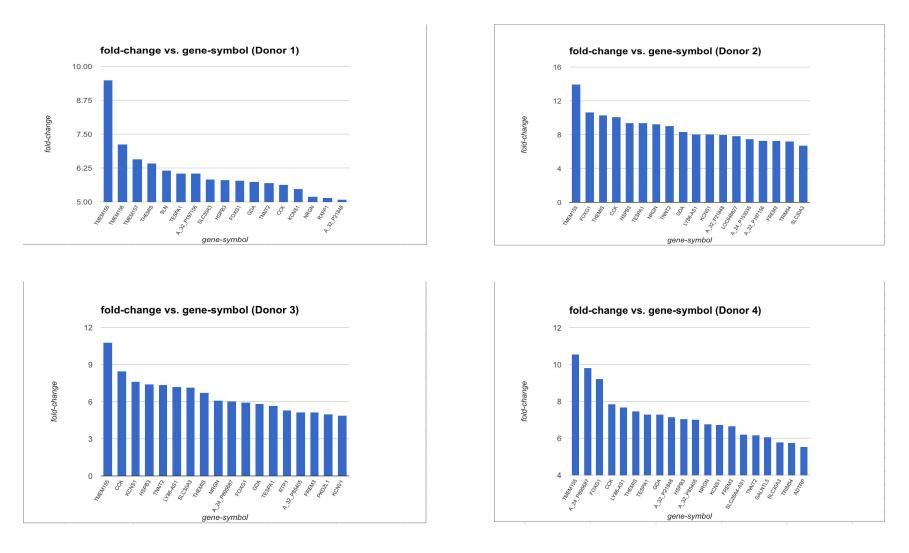
The microarray heat map shows the gene expression data of the frontal lobe compared to gray matter, for 6 different donors. The bar on the top of the map shows each of the 6 donors, and the bar beneath it displays sub-regions of the frontal lobe. The red portions of the map show genes that are over represented, and the green parts show genes that are under represented. The black regions depict no difference. Areas of high expression in the frontal lobe relative to gray matter include the frontal gyrus, temporal lobe, occipital lobe, and parietal lobe

## **Common Genes**



A venn diagram was used to determine common genes among the 4 donors. The results revealed that there were 63 (35.4%) common genes between all 4 donors. Donors 1, 2 and 4 share 19 (10.7%) common genes, and donors 2, 3 and 4 share 18 (10.1%) common genes.

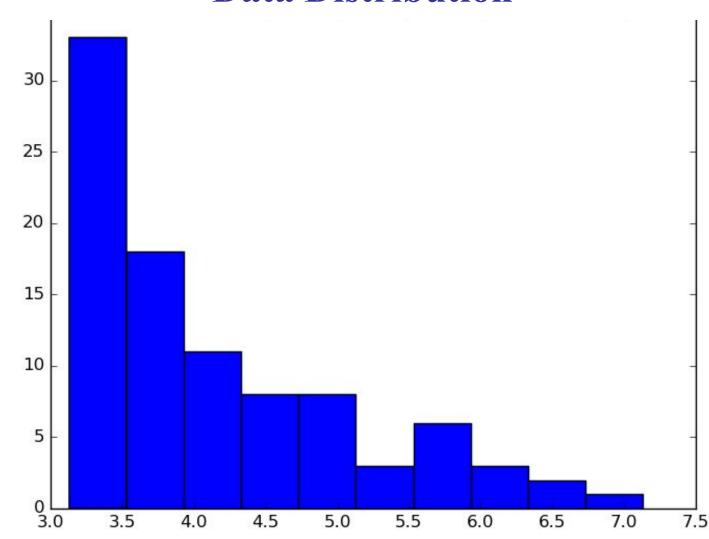
### **Top 20 Genes with Highest Expression Values**



The y-axis shows the fold-change values and the x-axis displays the gene symbols. Among the 4 donors, each have 10 common genes in their first 20 highest expressed genes. The gene, TMEM155, has a significantly higher fold-change value for all 4 donors, while the rest of the values onwards seem to have a linear negative rate.

10 Common Genes: TMEM155, THEMIS, SLC30A3, NRGN, KCNS1, HSPB3, GDA, TNNT2, FOXG1, CCK

# **Data Distribution**



This data distribution is representative of the all the data sets considered in the study. This histogram is right skewed. The x-axis shows the fold-change values, and the y-axis shows the frequency of each fold-change value. The majority of the data falls below 7.0 fold-change.

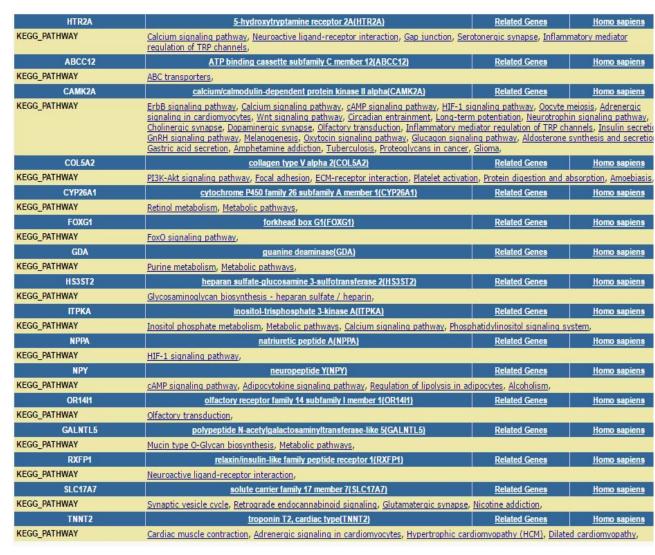
#### **Statistical Analysis**

stats					
	fold chang	e 1 fol	d change 2	fold change 3	fold change 4
count	93.000	000	93.000000	93.000000	93.000000
mean	4.142	688	5.502667	4.132527	4.762516
std	0.948	757	1.641066	1.192746	1.323614
min	3.130	000	3.895000	3.134000	3.501000
25%	3.380	000	4.401000	3.351000	3.858000
50%	3.850	000	4.939000	3.665000	4.275000
75%	4.710	000	6.120000	4.246000	5.055000
max	7.130	000	10.639000	8.500000	9.813000
varian	ce				
fold c	hange 1	0.900139			
fold c	hange 2	2.693098			
fold c	hange 3	1.422644			
fold c	hange 4	1.751955			
dtype:	float64				
>>>					

The mean fold-change for the donors 1, 3, and 4 are relatively similar, however the mean for donor 2 is slightly higher. The minimum values for all of the donors are similar, while the maximum values for the 4 donors are all different. The standard deviation for all of the donors are close in value to their corresponding mean fold-change values which indicates that the data is spread out.

#### **Common Gene Classification**



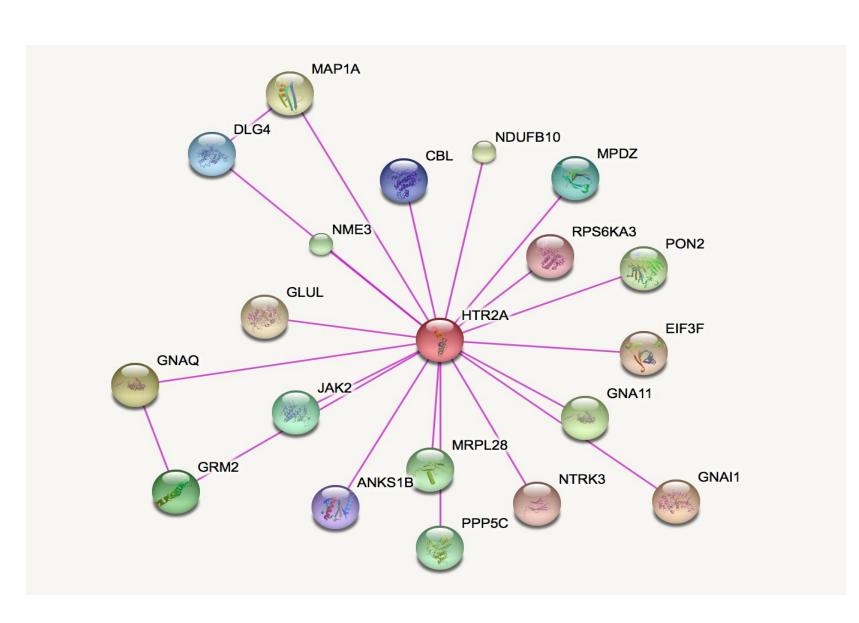


The next goal was to determine relevant candidate genes among the common genes of all 4 donors. Using gene ontology classification, there were 15 genes found to be associated with neural processes:

# HTR2A, FEZF2, SATB2, CAMK2A, CCK, ENC1, HSPB3, NPPA, NRGN, NEUROD6, NPY, OVOL2, RXFP1, SLC17A7, and SLC30A3.

The neural processes were found to be related to behavioral pathways such as locomotion and fear response. There were 2 genes associated with Schizophrenia and there was a common correlation in the genes for a predisposition for addiction.

## **Network Analysis**



HTR2A: Schizophrenia, OCD, susceptibility to Anorexia nervosa, seasonal affective disorder, behavioral response to cocaine NDUFB10: Alzheimer's, Parkinson's, Huntington's DLG4: social behavior, exploration behavior, grooming, Huntington's disease, cocaine addiction GNAQ: Alzheimer's, Huntington's, maternal behavior PPP5C: Alzheimers RPS6KA3: mental retardation

\*gene symbols highlighted in red indicate that they are in a cluster as shown in the corresponding network images. Clusters are interconnected regions that show that genes function in the same pathway.

Clusters: DLG4 and MAP1A; GNAQ and GRM2.

**GRM2:** cocaine addiction

RGS2: Schizophrenia, panic disorder
CALM1: Alzheimer's
PRKCG: chemosensory behavior, amphetamine, morphine addiction
ADCY5: locomotory, cocaine amphetamine, morphine addiction
GNAQ: Alzheimer's, Huntington's, maternal behavior, Schizophrenia
LRRK2: exploratory behavior, Parkinson's
GNAS, CALM1: amphetamine addiction

PRKCA, PRKCB: amphetamine, morphine addiction

\*gene symbols highlighted in red indicate that they are in a cluster as shown in the corresponding network images. Clusters are interconnected regions that show that genes function in the same pathway.

Clusters: COPB1 and COPB2; GNAQ, GNAS and ADCY5; IBTK, PRKCB and PRKCG; PRKCA, GNA15 and PRKG1.

# **Conclusions**

- Like most mental disorders, bipolar disorder is quite challenging to diagnose as it often gets misdiagnosed as depression or ADHD because of its abrupt lows and hysteric highs.
- characteristic delusional thinking and loss of touch with reality.

  Those with bipolar disorder often have abnormal levels of serotonin, dopamine an

Schizophrenia is also commonly associated with bipolar disorder because of the

- Those with bipolar disorder often have abnormal levels of serotonin, dopamine and norepinephrine which leads to unstable moods and emotions.
- \* Many individuals who experience these unbalanced emotions turn to alcohol or drugs in heavy doses as a means to cope with their erratic behavior. However, in most cases, these substances only make the symptoms of bipolar disorder worse.
- The genes that are associated with bipolar disorder are also commonly linked with addiction, confirming one's inclination to turn to substance abuse when dealing with this disorder.