

Identifying Candidate Genes for PTSD

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Introduction

- Post-Traumatic Stress Disorder (PTSD) is an anxiety disorder in which a person cannot fully recover from a traumatic event.
- Symptoms experienced include anxiety, flashbacks, sleeping disorders, depression, increased startle reflex, mood swings, and suicidal thoughts or actions.
- The basal ganglia is a region of the brain associated with PTSD.
- For this project we examined gene expression patterns in the basal ganglia to identify candidate genes for PTSD.

Methods

Gene expression data for the basal ganglia was collected from the Allen Brain Atlas (<http://www.brain-map.org>) using the differential search option. Data was collected from four available donors: H0351.1009, H0351.1015, H0351.1016, H0351.2001

Venny 2.1.0 (<http://bioinfogp.cnb.csic.es/tools/venny>) was used to compare the gene lists to identify genes common across the four donor brains.

Statistical analysis was done in Python Anywhere, an online programming tool (<http://www.pythonanywhere.com>)

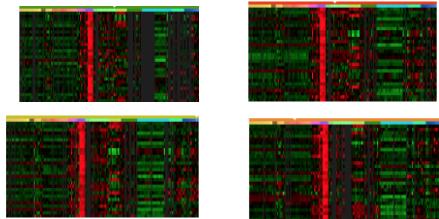
Cluster analysis and Gene Ontology classifications were obtained with DAVID (<https://david.ncifcrf.gov>)

The STRING database (<http://string-db.org>) was used to identify potential interacting genes related to PTSD using experimental data from genetic and biochemical studies. No experimental data was available for PENK so textmining was used.

GeneWeaver (<http://www.geneweaver.org>) was also used to find further supporting information for relevant genes.

Results

Gene Expression Profiles



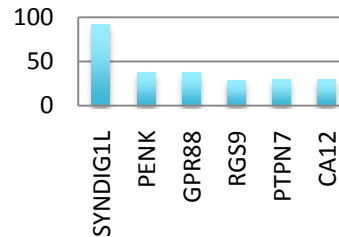
The heat maps show microarray data for gene expression of the basal ganglia compared to gray matter for the four donors (left to right): H0351.1009, H0351.1016, H0351.1015, H0351.2001). The red indicates an expression greater than the control, the green indicates an expression less than the control, while the black indicates an equal expression. Data with a fold expression of 3 or above was used for the analysis.

Common Genes



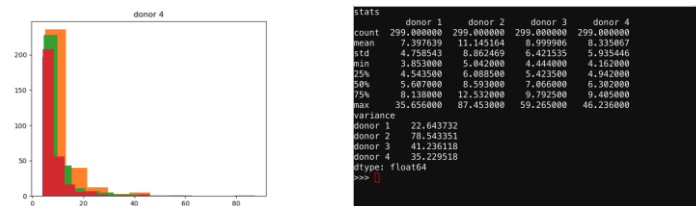
85 genes (44.3%) were common across all four donors.

Top 20 Genes with Highest Expression Values



The y-axis shows the fold-change values and the x-axis displays the gene symbol. The genes displayed are the genes in the top 20 with the highest expression values: SYNDIG1L, PENK, GPR88, RGS9, PTPN7, and CA12.

Data Distribution and Statistical Analysis



The data distribution shows all the data sets considered in the analysis across the four donors. The graph is heavily right skewed and is similar between the four donors. The y-axis shows the frequency and the x-axis shows the fold-change values.

The mean fold-change for donors 1, 3, and 4 are similar while the mean fold-change for donor 2 is relatively higher. Likewise, the minimum and maximum values for donors 1, 3, and 4 are similar while donor 2 is significantly higher. The standard deviation for all four donors is relatively close to their mean fold-change as well.

Common Gene Classification

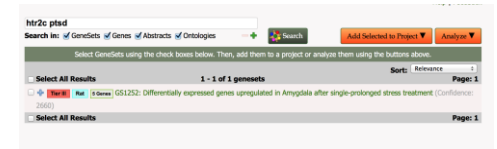
Cluster(s)	Gene(s)	Enrichment Score	Count	P-Value
1	OUTER_MF_DIRECT	response to environmental stimulus	7	6.00E-4
2	SMAD7		7	1.60E-4
3	OUTER_MF_DIRECT	defense response to bacterium	4	1.90E-3
4	OUTER_MF_DIRECT	response to hypoxia	4	2.00E-3
5	NEGL_PATHWAY	MAPK signaling pathway	8	3.20E-3
6	OUTER_MF_DIRECT	stress response	5	3.80E-3
7	NEGL_PATHWAY	cytoskeleton reorganization	6	3.90E-3
8	OUTER_MF_DIRECT	response to hypoxia	7	4.10E-3
9	OUTER_MF_DIRECT	response to hypoxia	7	4.10E-3
10	OUTER_MF_DIRECT	response to hypoxia	7	4.10E-3
11	NEGL_PATHWAY	response to hypoxia	7	4.10E-3
12	NEGL_PATHWAY	response to hypoxia	7	4.10E-3
13	NEGL_PATHWAY	response to hypoxia	7	4.10E-3
14	NEGL_PATHWAY	response to hypoxia	7	4.10E-3
15	NEGL_PATHWAY	response to hypoxia	7	4.10E-3
16	NEGL_PATHWAY	response to hypoxia	7	4.10E-3

Candidate genes were determined across the four donors. Using gene ontology classification, the genes PENK, DRD2, and HTR2C were determined to be associated with relevant brain processes. PENK is associated with fear regulation and aggression; DRD2 is associated with pre-pulse inhibition and dopamine production; and HTR2C is associated with serotonin production, fear, and locomotion. All of these are connected to behaviors and experiences resulting from PTSD.

Network Analysis



The genes examined in STRING were (from left to right): DRD2, PENK (textmining), and HTR2C. The associated genes have similar correlations to PTSD.



Using GeneWeaver, HTR2C was the only gene found to be associated with PTSD from previously published data in a study that examined amygdala gene expression in stressed individuals. *Pharmacology, biochemistry, and behavior*, Mar 2008, Vol 89, pp. 11-6

Conclusions

- The relevant genes all had interconnectivity.
- HTR2C, DRD2, and PENK are all associated with symptoms and behaviors related to PTSD, but the only one with a direct known correlation thus far is HTR2C.
- HTR2C is associated with stress and is also found in the amygdala, a region of the brain which controls the fight-or-flight response and is also associated with PTSD.
- The relevant genes found were often associated with serotonin and dopamine production and regulation which are both connected to mood regulation.
- Additionally, relevant genes also were often associated with fear regulation and locomotion.