Huntington's Disease and the Basal Ganglia

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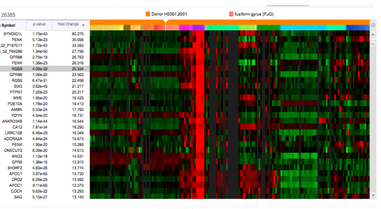
Background

- Huntington's Disease is a genetic disease that breaks down the nerves in the brain.
- Symptoms of the disease can appear in ages 30 to 50 and it will affect a person's ability to think, eat, move, and speak. Symptoms may describes as having ALS, Parkinson's and Alzheimer's disease at the same time.
- HD can be broken down into three stages. The first is chorea and mood swings. The second is involuntary movements that can affect swallowing and speech. The final stage is when voluntary moment is completely lost, in which assistance is necessary and can result in death.
- The basal ganglia is a part of the brain that controls movement and works closely with the frontal lobe.

Methods

- *Allan Brain Atlas* (http://www.brain-map.org/) was used to collect gene expression data from the basal ganglia area in the brain. The data came from four donors. Donor one: H0351.2001; Donor two: H0351.2002; Donor three: H0351.1009; Donor four: H0351.1012. *Venny* (http://bioinfogp.cnb.csic.es/tools/venny/index.html) was used to sort through the genes found in the four donors to find all the genes that the donors had in common.
- *Python Anywhere* (https://www.pythonanywhere.com/) was used to create a chart showing the different fold changes in the genes taken from the four donors.
- *DAVID* (https://david.ncifcrf.gov/tools.jsp) is a functional annotation tool used to cluster different genes based on their function.
- *STRING* (http://string-db.org) is a database that was used to identify what proteins a specific gene interacts with.
- *Gene Wrangler* (https://geneweaver.org/index.php?action=search) was used to further investigate the relevance of genes found using the other databases to Huntington's Disease.

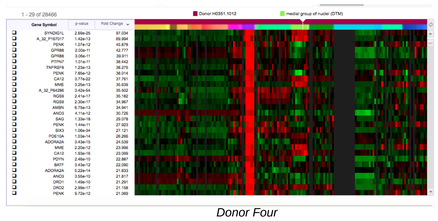
Results



Donor One

Donor Two

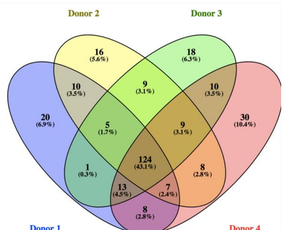
Donor Three



Donor Four

The heat maps above are collected from the basal ganglia region from four donors. The data collected needed the requirement of a fold change greater than 3. The red parts of the maps demonstrate high gene expression and the green express low gene expression. The black section represents equal expression.

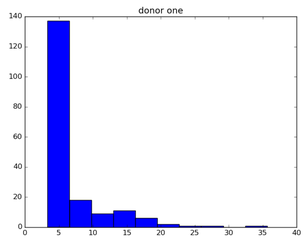
Common Genes



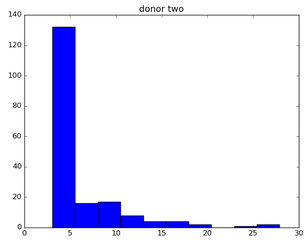
The Venny database was used to gather the selected genes from the four donors and compare them to see which genes were found common in all of the donors. 43.1% of genes were common throughout the four donors.

Data Analysis

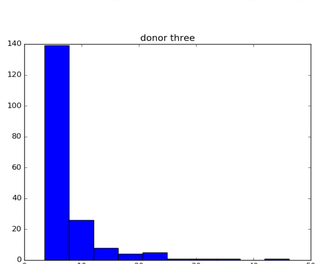
Python created a histogram showing the different fold changes in each of the four donors. The y-values display gene frequency, while the x-value displays the fold change of the genes.



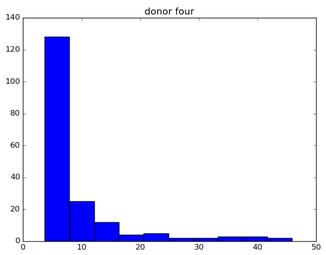
The histogram is heavily right-skewed for a smaller fold change. The frequency of genes with a fold change of about 5 is approximately 140.



The histogram is right-skewed. However, it is not as drastic as Donor One. Between fold change 6 and 10, the genes increase in frequency.



The variation in fold change is sizeable, displaying a heavily right-skewed graph. Genes with a larger fold change decrease at a value of approximately 25; however, after this point, the rest is minimal.



The fold-change variation is right-skewed but not as extreme, similar to Donor Two. However, around the 30 on the x-axis, the value decreases and returns to a stable fold change around 10 on the y-axis.

Statistical Analysis

```
stats
       donor one   donor two  donor three  donor four
count  186.000000  186.000000   186.000000  186.000000
mean     6.585790    5.904758     7.292220    9.018823
std      4.888095    4.377944     6.046246    8.218782
min      3.347000    3.072000     3.562000    3.729000
25%      3.802500    3.366500     4.074000    4.386250
50%      4.569000    4.033000     4.875500    5.595000
75%      6.812500    6.970500     7.772250    9.554000
max     35.656000   27.877000    46.236000   45.878000
variance
donor one      23.893479
donor two      19.166389
donor three    36.557890
donor four     67.547062
dtype: float64
>>>
```

The maximum fold change of all four donors varies, with Donor Two being the lowest (27.877) and Donor Three being the highest (46.238). However, the minimum fold change is very similar in all of the donors. The average ranges between 5 and 9, however, they are still around the same value. Standard deviation also has the same variance as the mean; it fluctuates between 4 and 8.

Common Gene Analysis

Submitting the list of the common genes from all four donors into DAVID showed their functions, which helps to determine their connection to Huntington's disease. Searching the list with keywords such as "behavior," "response," and "locomotor", two genes began to come up frequently. The genes are called PENK and SLITRK6.

These two genes, however, did not have any relation to physically reacting genes. Therefore, two newly refined gene lists needed to be searched in DAVID using keywords again. Once this was done, three genes appeared repeatedly. The three genes were HTR2C, DRD1, and DRD2.

PENK	proenkephalin(PENK)	Related Gene
GOTERM_BP_DIRECT	osteoblast differentiation, behavioral fear response, response to hypoxia, startle response, aggressive b neuropeptide signaling pathway, chemical synaptic transmission, aging, sensory perception, response t substance, glial cell proliferation, sensory perception of pain, response to estradiol, response to lipopol to oxidative stress, response to nicotine, locomotory exploration behavior, response to morphine, respo calcium ion, general adaptation syndrome, behavioral process, cellular response to vitamin D, cellular r response to transforming growth factor beta stimulus, response to epinephrine, cellular response to vir behavioral fear response,	
GOTERM_CC_DIRECT	extracellular region, plasma membrane, dendrite, symmetric synapse, neuronal cell body, perikaryon,	
GOTERM_MF_DIRECT	opioid peptide activity, neuropeptide hormone activity, opioid receptor binding,	
INTERPRO	Proenkephalin A, Opioid neuropeptide precursor,	
UP_KEYWORDS	3D-structure, Cleavage on pair of basic residues, Complete proteome, Disulfide bond, Endorphin, Neuro Phosphoprotein, Polymorphism, Proteomics identification, Reference proteome, Secreted, Signal,	
UP_SEQ_FEATURE	disulfide bond, peptide:Leu-enkephalin, peptide:Met-enkephalin, peptide:Met-enkephalin-Arg-Gly-Leu, Phe, peptide:PENK(114-133), peptide:PENK(143-183), peptide:PENK(237-258), peptide:Synenkephalin variant, signal peptide,	

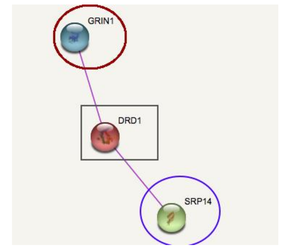
SLITRK6	SLIT and NTRK like family member 6(SLITRK6)	Related Gen
COG_ONTOLOGY	Function unknown,	
GOTERM_BP_DIRECT	startle response, lens development in camera-type eye, auditory receptor cell morphogenesis, axonog visual perception, sensory perception of sound, adult locomotory behavior, vestibulocochlear nerve de multicellular organism growth, positive regulation of synapse assembly, linear vestibulocular reflex, r development,	
GOTERM_CC_DIRECT	integral component of plasma membrane, cell surface,	
INTERPRO	Cysteine-rich flanking region, C-terminal, Leucine-rich repeat, Leucine-rich repeat, typical subtype,	
OMIM_DISEASE	Deafness and myopia,	
SMART	LRRCT, LRR_TYP,	
UP_KEYWORDS	Cell membrane, Complete proteome, Deafness, Hearing, Leucine-rich repeat, Membrane, Polymorphis Sensory transduction, Signal, Transmembrane, Transmembrane helix, Vision,	
UP_SEQ_FEATURE	chain:SLIT and NTRK-like protein 6, modified residue, repeat:LRR 1, repeat:LRR 10, repeat:LRR 11, r repeat:LRR 14, repeat:LRR 15, repeat:LRR 16, repeat:LRR 2, repeat:LRR 3, repeat:LRR 4, repeat:LR repeat:LRR 8, repeat:LRR 9, sequence conflict, sequence variant, signal peptide, topological domain:C domain:Extracellular, transmembrane region,	

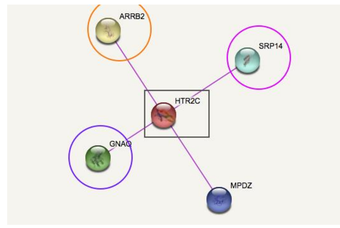
Network Analysis

The STRING database is used to show how a specific gene interacts with other proteins. Taking the three new ge DRD1, and DRD2) and placing them into STRING, there was a similar gene that was shown to interact in all three gene is SRP14. The three main genes were used as "fish hooks" to search for more genes related to the behavior Gene Wrangler helped to learn more about the genes found in STRING and what their relationship to Huntington's

GRN1- has a direct relation to Huntington's disease; can correlate to abnormal fear, feeding, and social behavior

SRP14- gene involved with the hippocampus and locomotor behavior; common gene in HD





PAWR- no direct relationship to HD; behavioral p men and women; connected to behavioral despa

GNAI2- relates to many sensitivity responses, su or anxiety

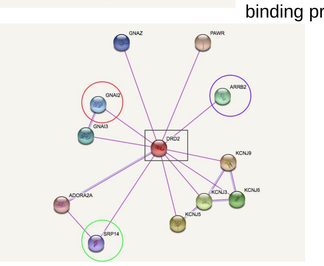
ARRB2- common in HTR2C; relation to walking b response

SRP14- common gene found between HTR2C, D binding protein

ARRB2- common gene found in DRD2; relation to walking and stress response

GNAQ- this binding protein has a relationship to HD based on its geneset in the "Huntington's dieses" pathway

SRP14- common gene between HTR2C, DRD1, and DRD2; a binding protein



Conclusion

- The Basal Ganglia contained many genes that deal with the locomotor and behavioral functions of Huntington's dise
- Genes such as HTR2C, DRD1, and DRD2 play a function in connecting many genes together that result in the beha is HD.
- Other diseases, such as ALS, Alzheimer's, and Parkinson's share similar functional traits to Huntington's because th same genes sets that produce similar actions when the disease is present.