

Identifying Candidate Genes for Aggressive Behavior

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Introduction

- The Ventral Medial Hypothalamic Nucleus (VMH) is a region of the brain that is associated with aggressive behavior.
- Aggressive behavior can entail uncommon social behaviors, locomotive reactions, mating, as well as fear, depression, anxiety, and stress.
- The VMH, a nucleus located towards the middle of the brain, is also involved with food satiety, temperature regulation, fear response, and sexual activity
- For this project, we examined gene expression patterns in the VMH to identify potentiation candidate genes linked to aggressive behavior

Methods

Gene expression data for VMH was collected from the The Allen Brain Atlas (<http://www.brain-map.org>) using the differential search option. Data was collected from four available donors: H0351.2002, H0351.1009, H0351.1012, H0351.1016

A correlation analysis was also performed in The Allen Brain Atlas using the correlation function that examines gene expression patterns that are similar to a candidate gene in a brain region of interest.

Venny 2.1.0 (<http://bioinfo.cnb.csic.es/tools/venny/>) 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

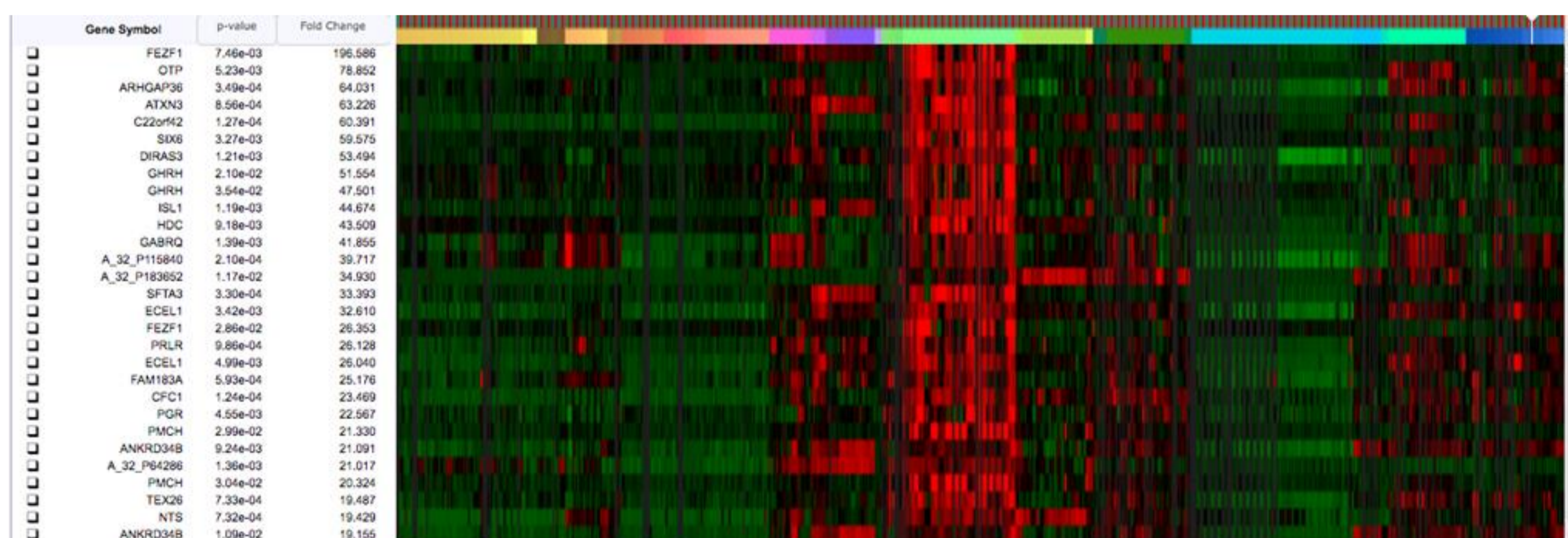
Cluster analysis and Gene Ontology classifications were obtained with DAVID (<https://david.ncifcrf.gov>)

The STRING database (<http://string-db.org>) was used to look for physical interactions between genes related to aggression using experimental data from gene studies.

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

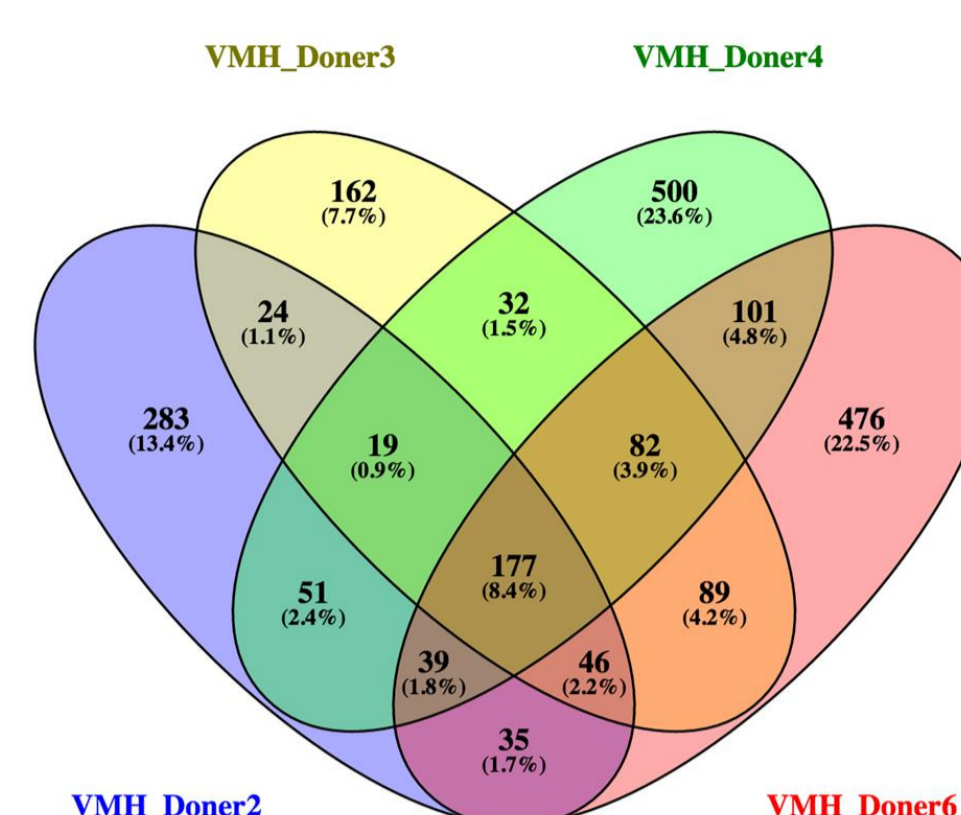
Results

Gene expression profiling



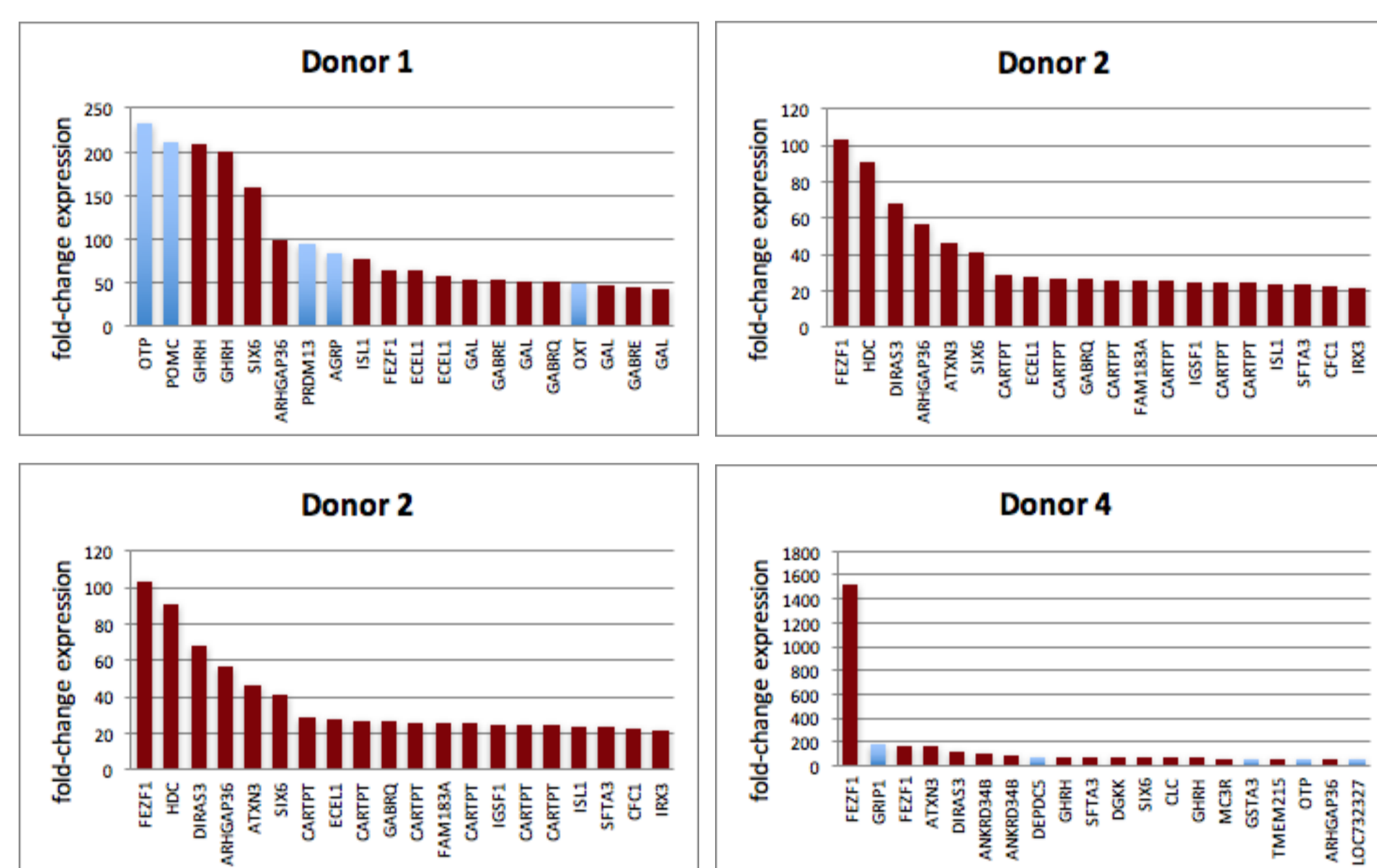
A heat map of the Affymetrix data shows the gene expression pattern in the VMH relative to gray matter for 6 donor brains. The top colored bar represents each donor. The bar below shows subregions of the VMH. There is high conservation of gene expression in the mammillary region which is comprised of the mammillary body, posterior hypothalamic area, supramammillary nucleus and tubulomammillary nucleus. Red = expression greater than control, Green = expression less than control, Black=expression equal to control. Data with a 3.0-fold expression and above were considered in the analysis

Common genes



8.4% of the the genes in the VMH are common between the 4 donors

Top 20 Genes with highest expression values



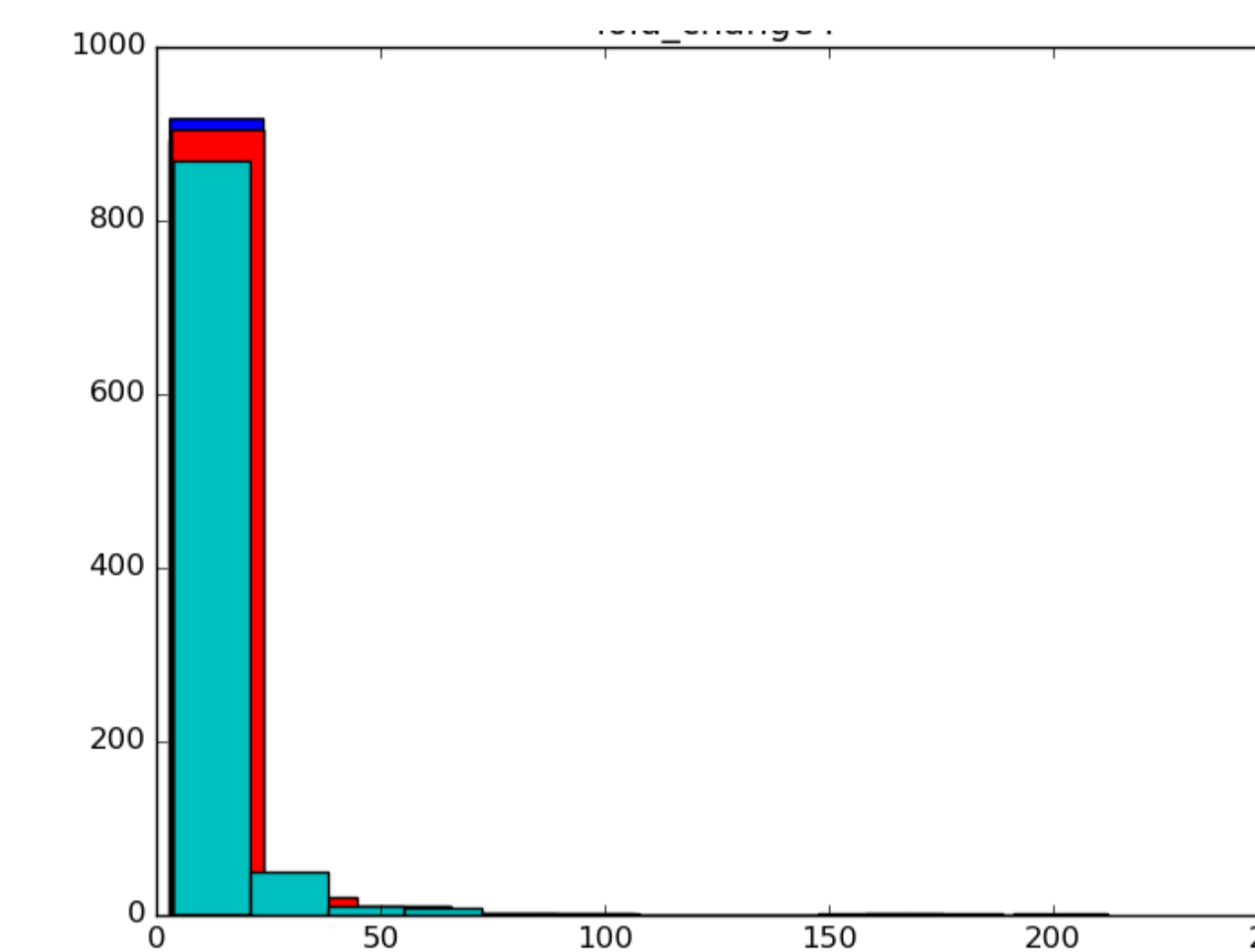
Most of the genes with the highest fold-expression values were conserved across all 4 donors (red) and are associated with regulatory functions, signaling, transport, and development. Few genes were uniquely expressed (blue).

Statistics

| stats | donor1 | donor2 | donor3 | donor4 |
|----------|------------|------------|------------|------------|
| count | 946.000000 | 946.000000 | 946.000000 | 946.000000 |
| mean | 7.715246 | 5.736192 | 8.715644 | 10.171171 |
| std | 15.072025 | 5.574404 | 15.331747 | 13.716066 |
| min | 3.078000 | 3.000000 | 3.546000 | 3.964000 |
| 25% | 3.566000 | 3.408500 | 3.987500 | 4.687250 |
| 50% | 4.469000 | 4.139500 | 4.830500 | 6.186500 |
| 75% | 6.511500 | 5.918000 | 7.931250 | 9.727500 |
| max | 212.118000 | 91.216000 | 209.258000 | 175.371000 |
| variance | | | | |
| donor1 | 227.165949 | | | |
| donor2 | 31.073982 | | | |
| donor3 | 235.062478 | | | |
| donor4 | 188.130456 | | | |

The gene expression data for Donor 2 has less variation than for the other datasets. The means for Donors 1, 3, and 4 data are in the same range whereas for Donor 2 it is ~2-fold lower. Comparison of the standard deviation (std) follows the same pattern as the means i.e. the std for donor 2 is lower than for the other datasets.

Data distribution



The overall distribution for the gene expression data is right-skewed. Most of the fold-change values fall below ~5 (fold change) whereas few genes are highly expressed.

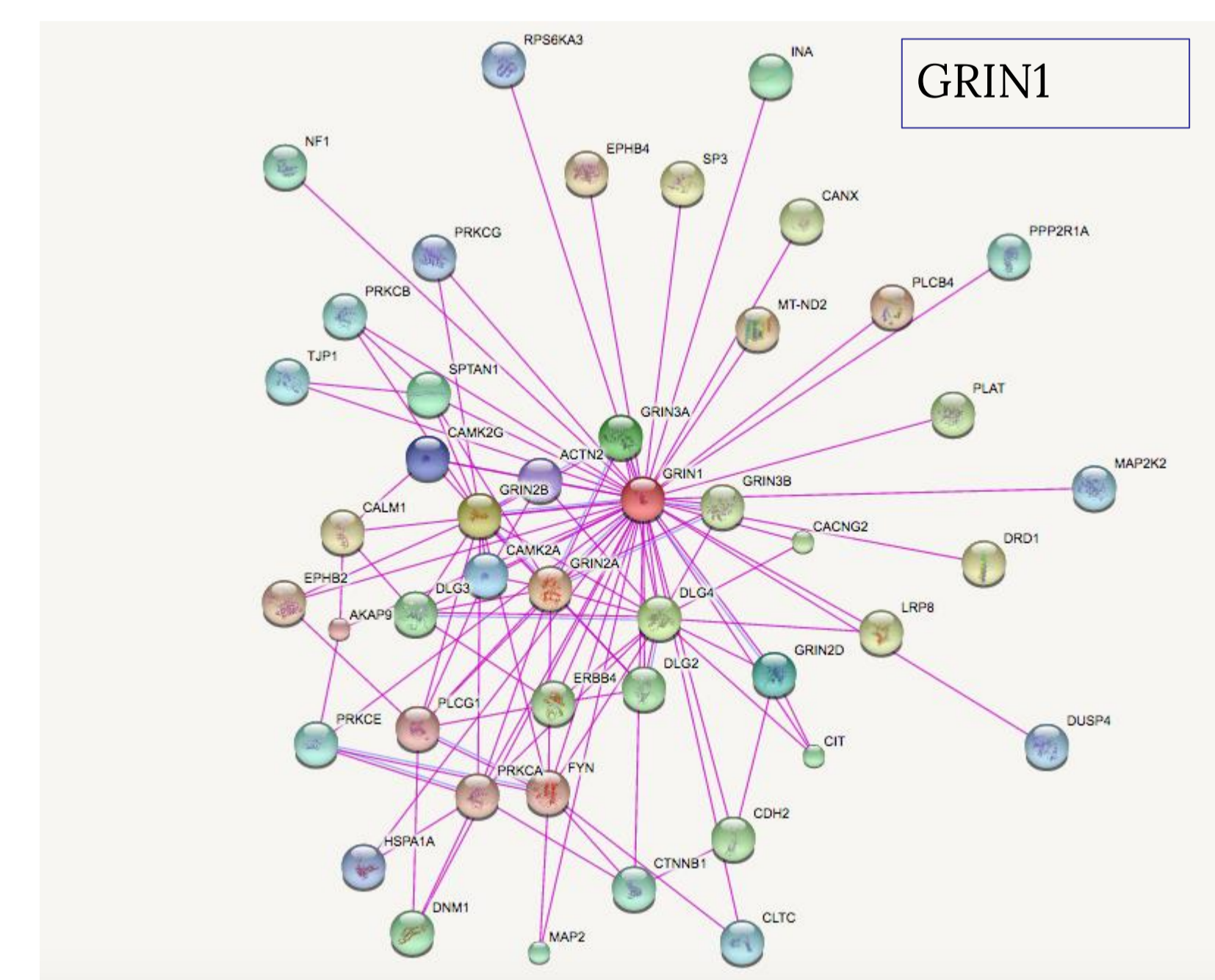
Candidate gene analysis

| MAOA | monoamine oxidase A | Related Genes | Homo sapiens |
|---------------|--|---------------|--------------|
| GOTERM_BP_FAT | regulation of neurotransmitter levels, cellular amino acid derivative metabolic process, biogenic amine metabolic process, catecholamine metabolic process, cellular signaling, synaptic transmission, behavior, amine catabolic process, catechol metabolic process, phenol metabolic process, transmission of nerve impulse, catechol catabolic process, diol metabolic process, diol catabolic process, neurotransmitter metabolic process, neurotransmitter catabolic process, cellular amino acid derivative catabolic process, biogenic amine catabolic process, dopamine metabolic process, dopamine catabolic process, catecholamine catabolic process, alcohol catabolic process, neurological system process, synaptotagmin regulation | | |
| GOTERM_CC_FAT | mitochondrion, mitochondrial envelope, mitochondrial outer membrane, plasma membrane, internal side of plasma membrane, internal to membrane, outer membrane, organelle membrane, intrinsic to membrane, mitochondrial membrane, organelle envelope, organelle outer membrane, envelope, mitochondrial, and plasma membrane part | | |
| GOTERM_MF_FAT | amine oxidase activity, electron carrier activity, oxidoreductase activity, acting on the CH-NH2 group of donors, oxidoreductase activity, acting on the CH-NH2 group of donors, oxygen as acceptor | | |
| INTERPRO | Flavin-coenzyme amine oxidase, Amine oxidase | | |
| KEGG_PATHWAY | Glycine, serine and threonine metabolism, Arginine and proline metabolism, Histidine metabolism, Tyrosine metabolism, Phenylalanine metabolism, Tryptophan metabolism, Drug metabolism | | |
| OMIM_DISEASE | antisocial behavior, Brunner syndrome | | |

Gene ontology classification of the common genes across all donors resulted in just one gene, MAOA, with an association to aggressive behavior and mental retardation.

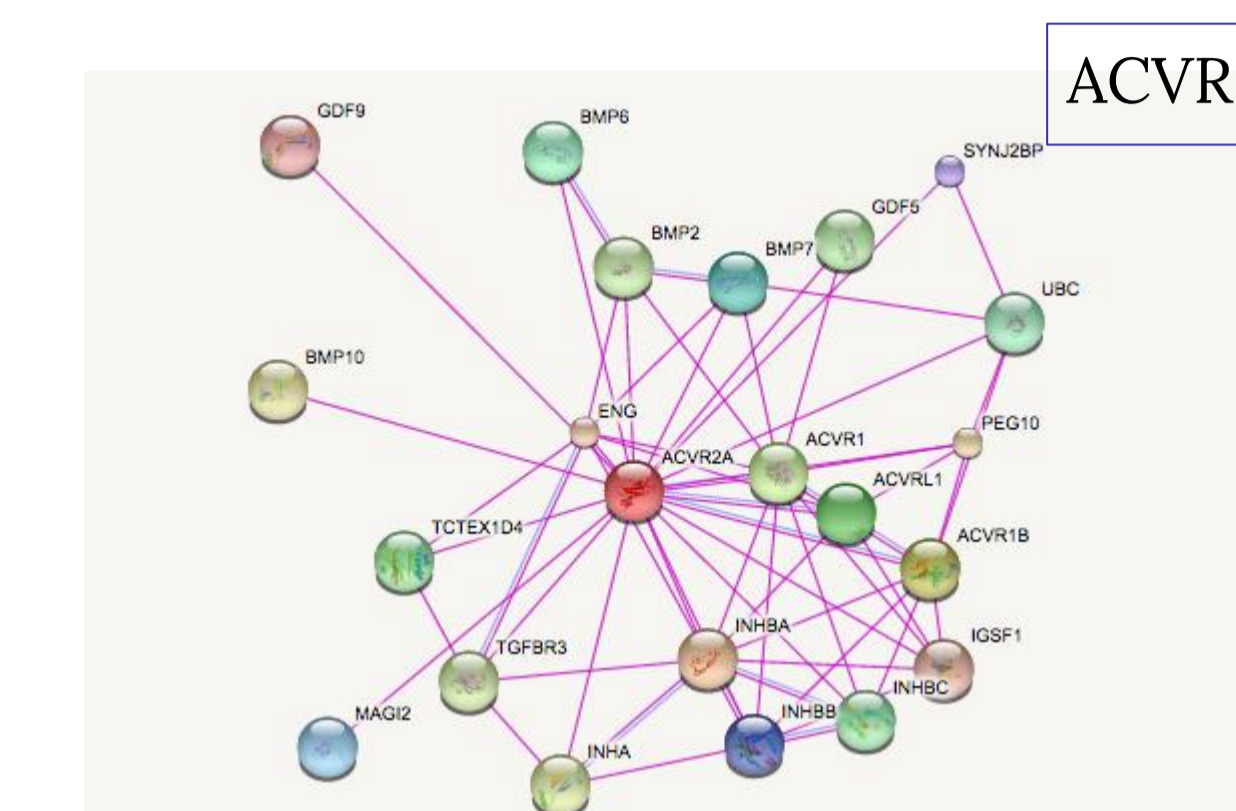
The MAOA gene was used in a subsequent correlation analysis to identify additional candidates in the VMH with the same gene expression pattern across all donors. 14 genes associated with neural processes and behavior were found. Four of these, in addition to MAOA, were strongly linked to aggressive behavior, fear/defense response (GABRA5, PENK) mating and olfaction (GRIN1, ACVR2A).

Network analysis



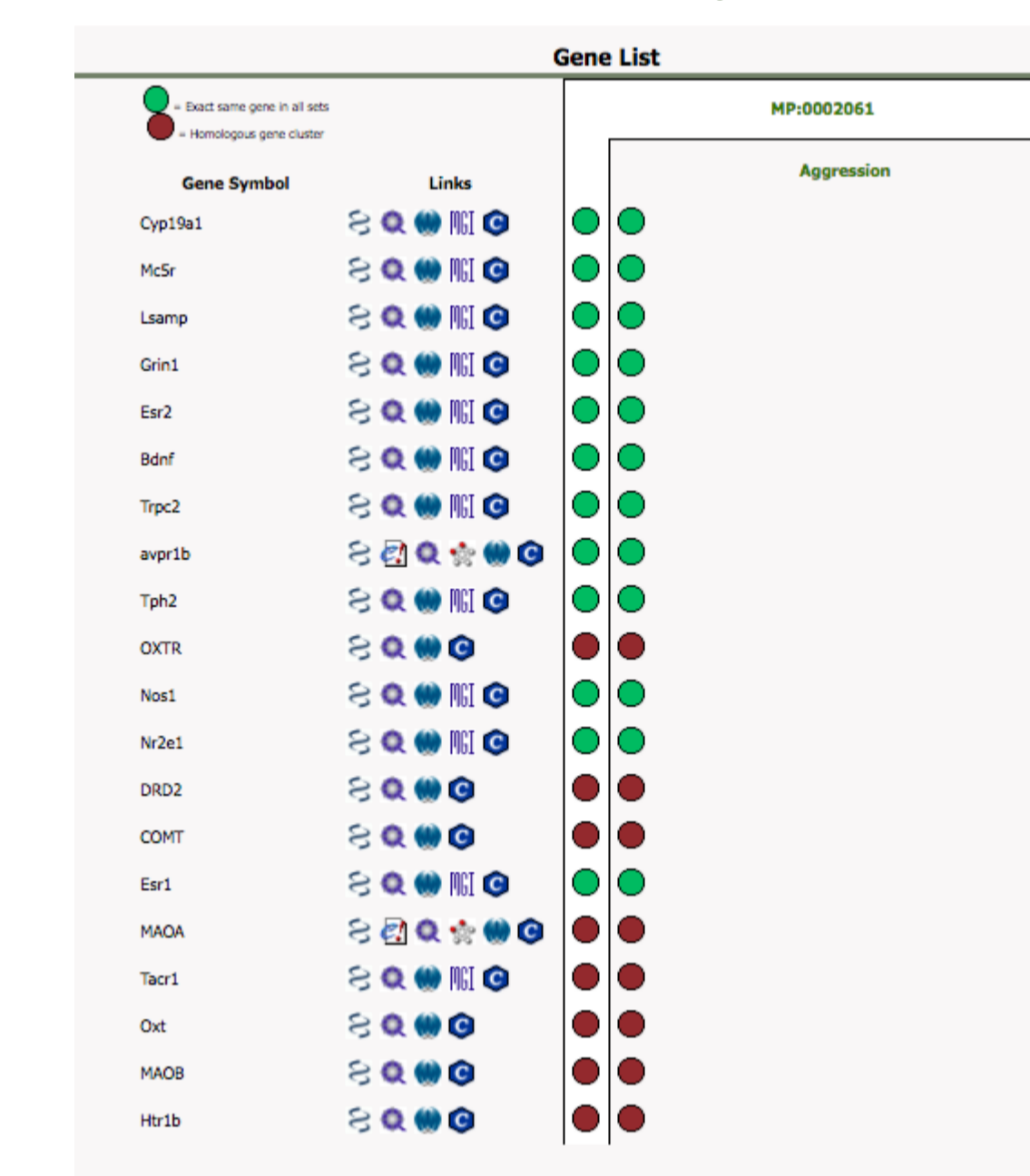
Relevant Genes:
Behavioral Fear Response- DRD1, GRIN2B
Mental Retardation-RPS6KA3, DLG3
Locomotion-ERBB4, PRKCA, NF1, GRIN2A, PRKCA

Network analysis (cont.)



ACVR2 gene network has a strong relation to regulation and signaling i.e. transcription factors, kinases, cytokines

Geneset analysis



There were 20 common genes expressed between two genesets associated with aggressive behavior using GRIN1 as a search term.

Gene Set #244021 Destructive behavior and verbal or physical attack, and hostility

Gene Set #169388 Abnormal aggression-related behavior such as assaultive, forceful physical action

Conclusions

Aggressive behavior is difficult to study because it is a combination of anxiety, fear, curiosity, hostility, and also associated processes like learning/memory and olfaction.

Of the genes identified in the differential and correlative analysis, MAOA and GRIN2 are most strongly linked to aggressive behavior.

The GRIN2 protein interaction network contains many proteins linked to social, locomotive behavior, fear, and mating. There was limited network information available for MAOA, GABRA5 and PENK.

The results from this analyses provide a rational basis for follow-up experimental studies to identify and validate genes linked to aggressive behavior.