

Systems Biology Module 1 Assignment

Mrinal Vashisth

GEO Datasets

The complete list of datasets can be found here:

<https://docs.google.com/spreadsheets/d/1k1r9aobxaEarWTcof-O6OICPDNP-Cf2AWMRaBaZ14EGk/edit?usp=sharing>

Following three datasets were selected:

GSE5389

Age effect on normal adult brain: frontal cortical region

GSE2879

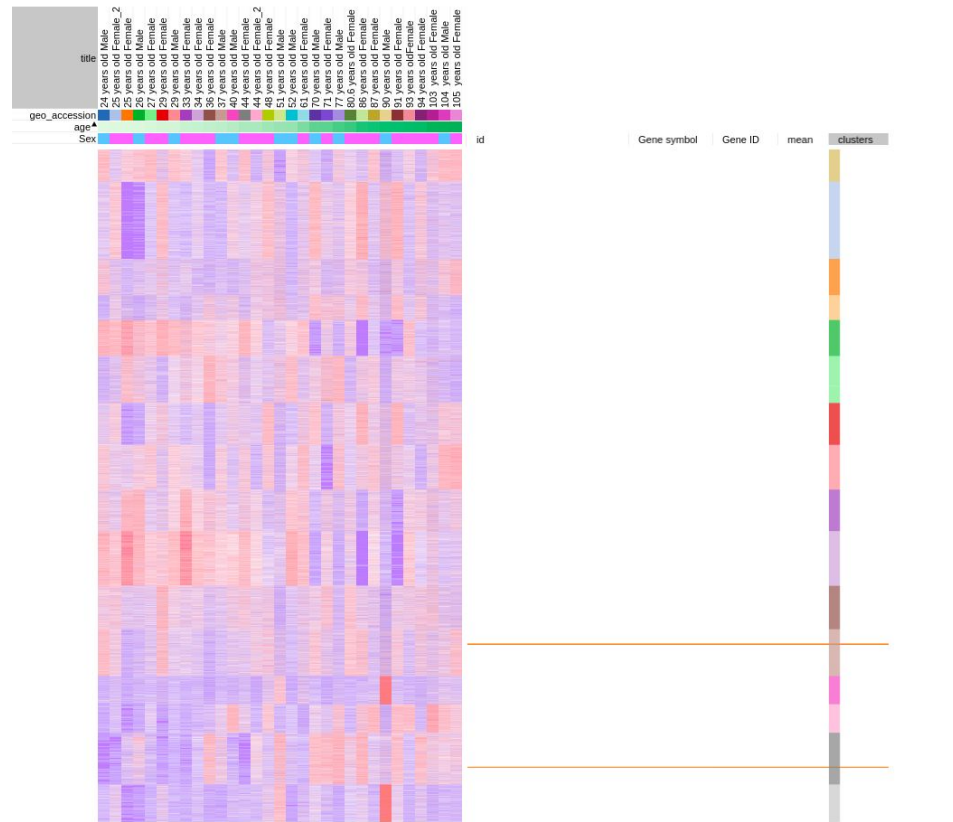
SIRT1 impact on global gene expression in the brain

GSE1940

Gene expression analysis of primitive neuroectodermal tumors

GSE53890 x

File Edit View Tools Help Rows Columns 54,675 rows by 41 columns 0 rows, 0 columns selected



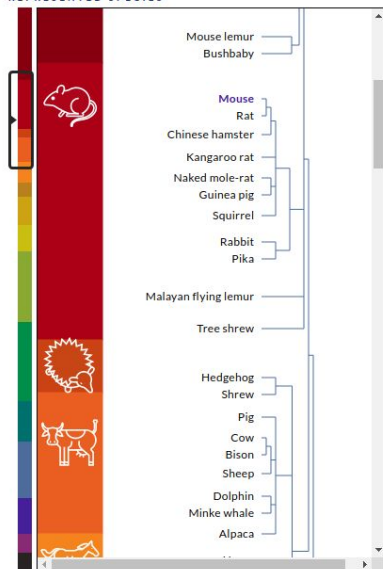
Browse/Select Species

POPULAR SPECIES



Enter species or common name

REPRESENTED SPECIES



Find Position

Mouse Assembly

Dec. 2011 (GRCm38/mm10)

Position/Search Term

Rest

Current position: chr5:77,265,494-77,283,697

GO

Mouse Genome Browser - mm10 assembly

[view sequences](#)

UCSC Genome Browser assembly ID: mm10

Sequencing/Assembly provider ID: Genome Reference Consortium Mouse Build 38 (GCA_000001635.2)

Assembly date: Dec. 2011

Accession ID: GCA_000001305.2

NCBI Genome ID: 52 (Mus musculus)

NCBI Assembly ID: 327618 (GRCm38/GCA_000001635.2)

NCBI BioProject ID: 20689



Mus musculus
(Photo courtesy of The Jackson Laboratory)

Other mice strains are available [here](#).

Search the assembly:

- **By position or search term:** Use the "position or search term" box to find areas of the genome associated with many different attributes, such as a specific chromosomal coordinate range; mRNA, EST, or STS marker names; or keywords from the GenBank description of an mRNA. [More information](#), including sample queries.
- **By gene name:** Type a gene name into the "search term" box, choose your gene from the drop-down list, then press "submit" to go directly to the assembly location associated with that gene. [More information](#).
- **By track type:** Click the "track search" button to find Genome Browser tracks that match specific selection criteria. [More information](#).

Download sequence and annotation data:

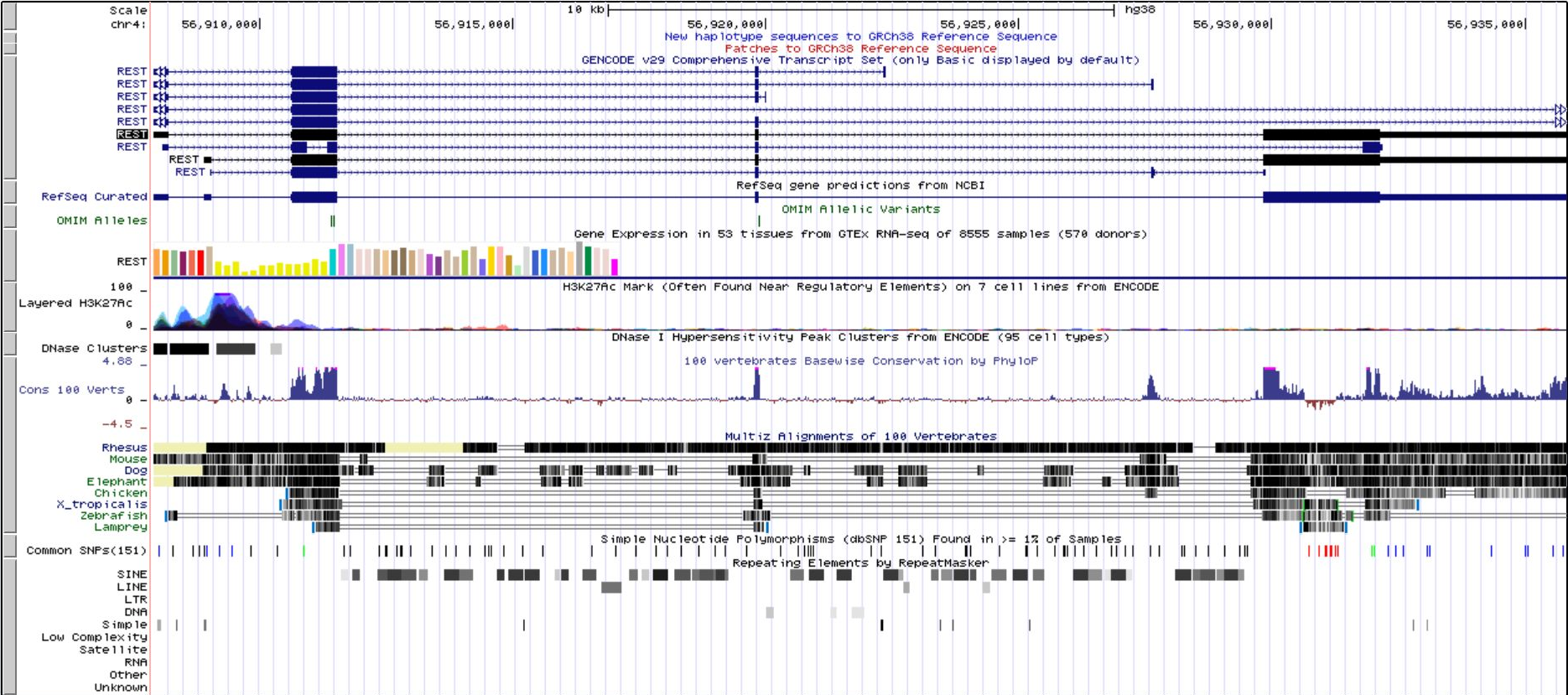
- Using rsync (recommended)
- Using FTP
- Using HTTP
- Data use conditions and restrictions
- Acknowledgments

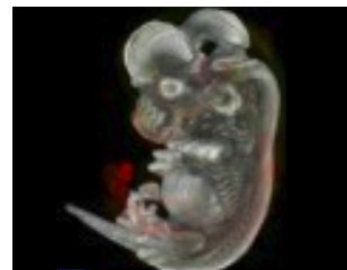
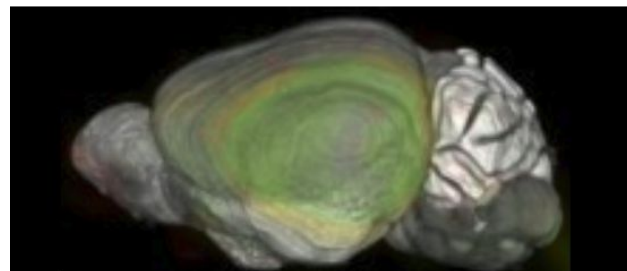
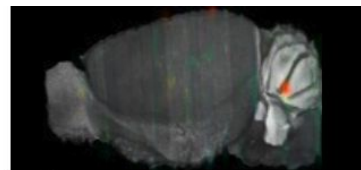
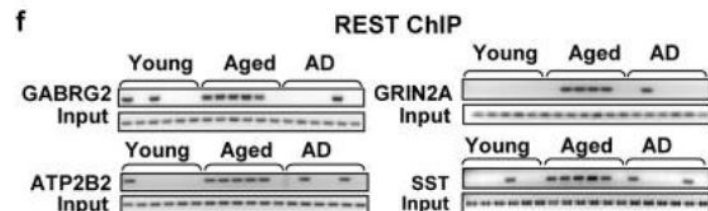
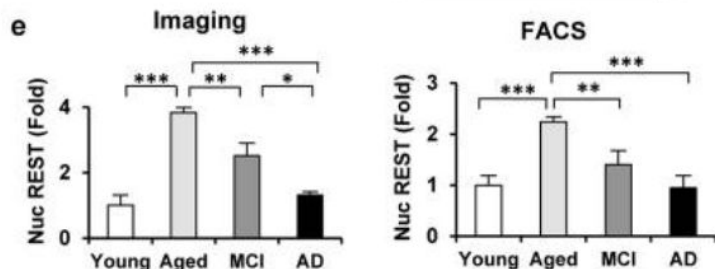
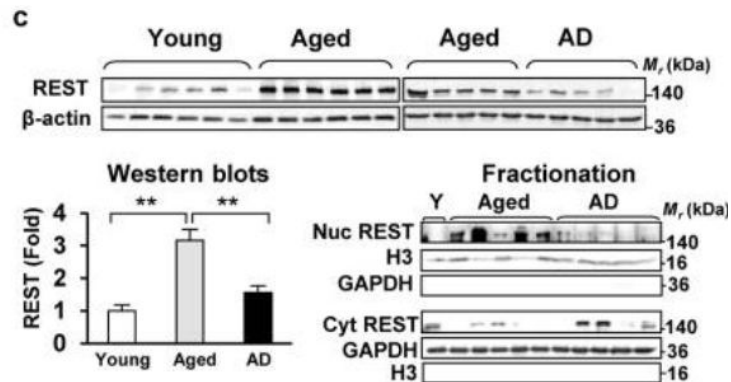
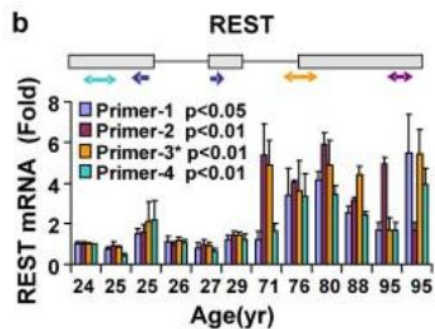
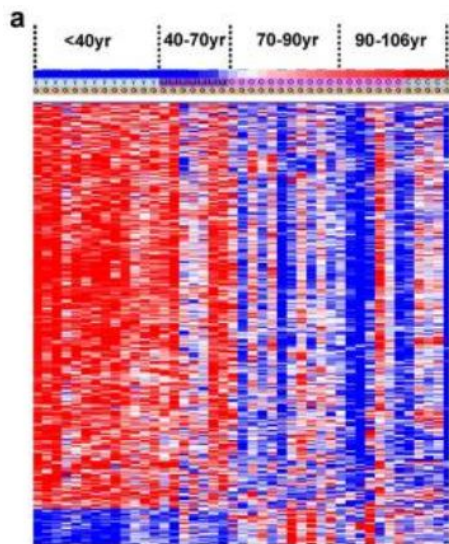
Assembly details

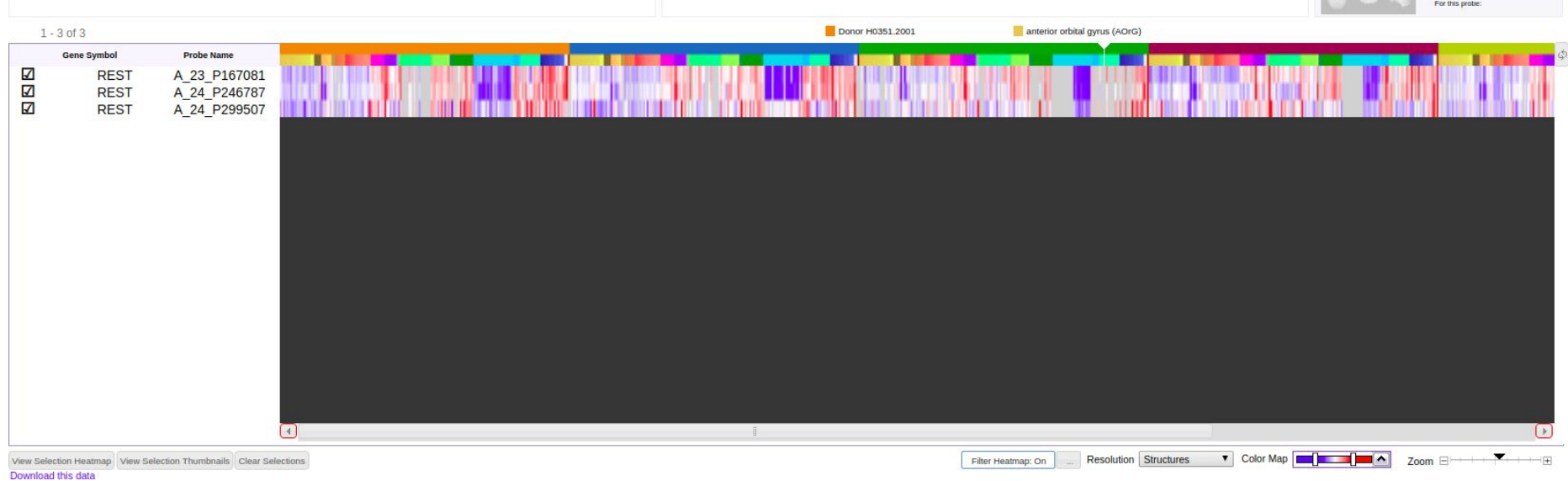
UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38) Assembly

move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x 100x

chr4:56,907,909-56,935,844 27,936 bp.





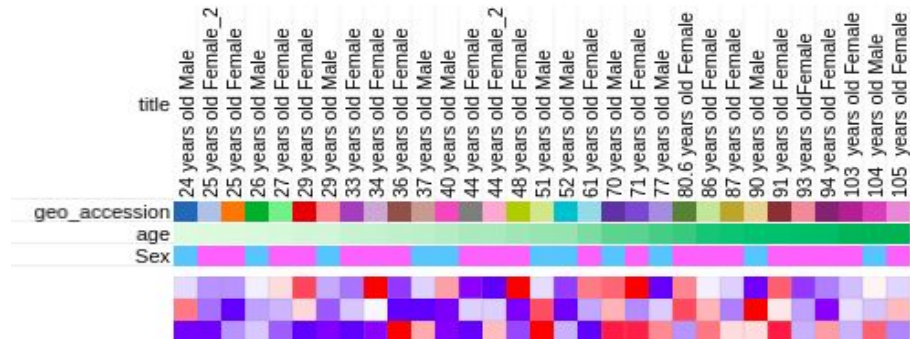


GSE53890 × GSE53890 × GSE53890 × GSE53890 ×

File Edit View Tools Help

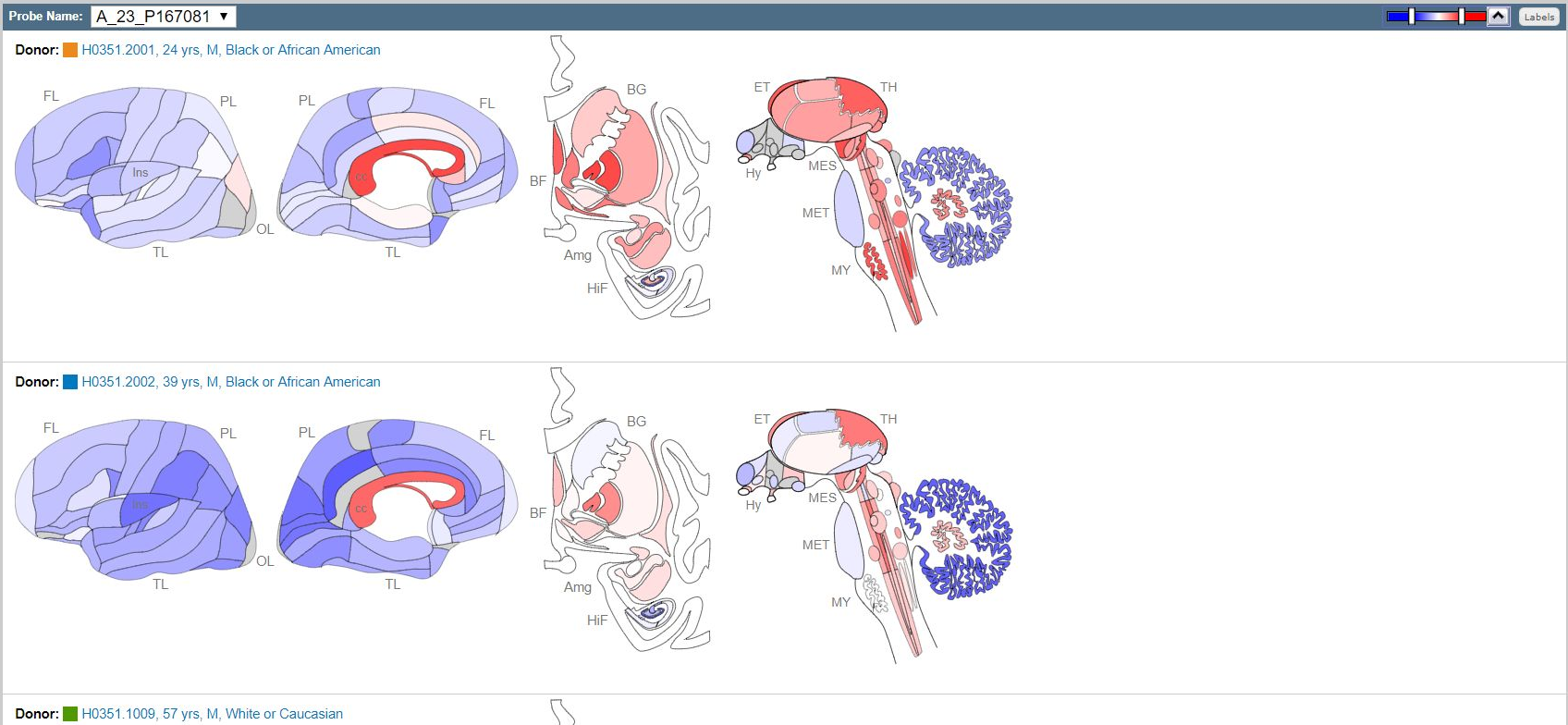
Rows Columns

3 rows by 31 columns 0 rows, 0 columns selected



id	Gene symbol	Gene ID	mean	clusters
204536_s_at	REST	5978	4.2683	
204535_s_at	REST	5978	6.2546	
212920_at	REST	5978	3.7054	

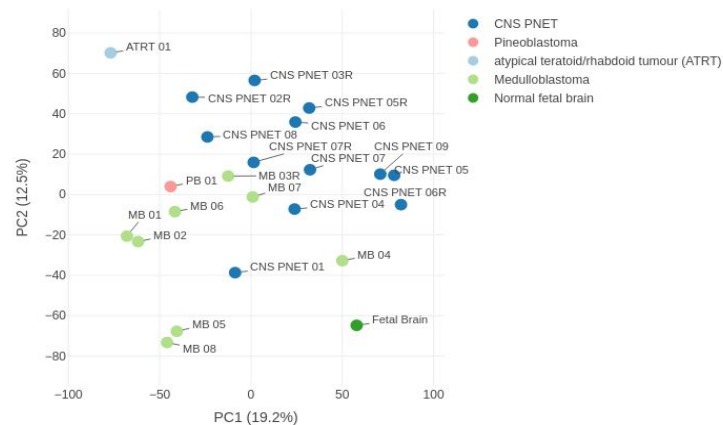
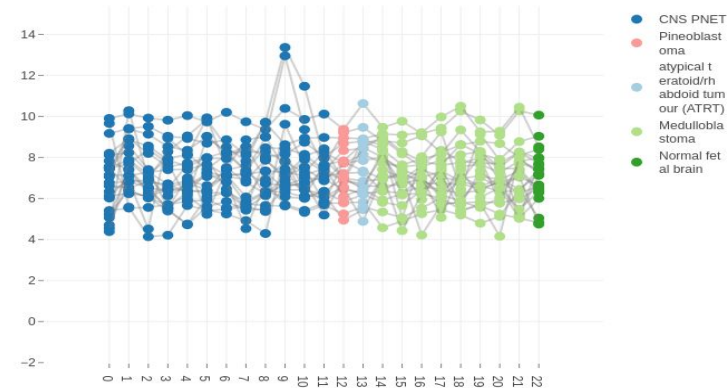
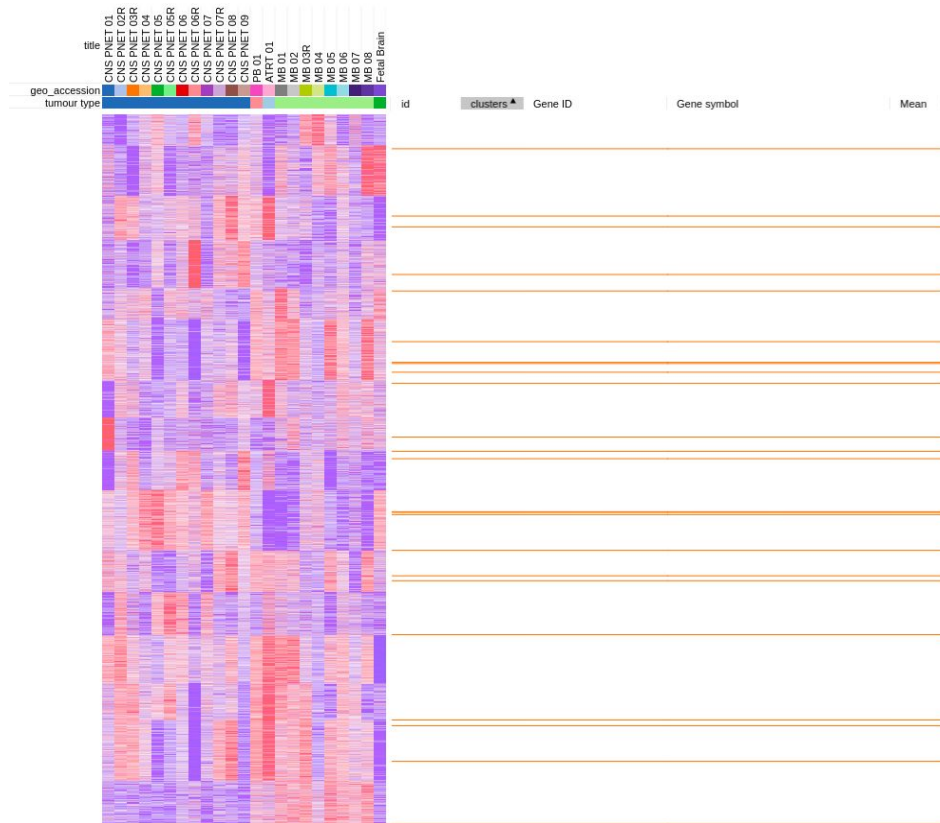
Gene REST			
Name	RE1-silencing transcription factor	Related Data	MOUSE HUMAN
Aliases	NRSF, XBR	Entrez ID	5978
Organism	Homo Sapiens	Chromosome	4
Probe A_23_P167081			
Probe Name	A_23_P167081	Probe Type	DNA
NCBI Accession	NM_005612.3	Transcript GI	15890082
Sequence Length	60	GC Percent	45
Sequence Data	ATCCACAGCCATGAAGGAAGTGACCTAAGTGACAACATGTCAGAGGGTAGTGATGATTCT		

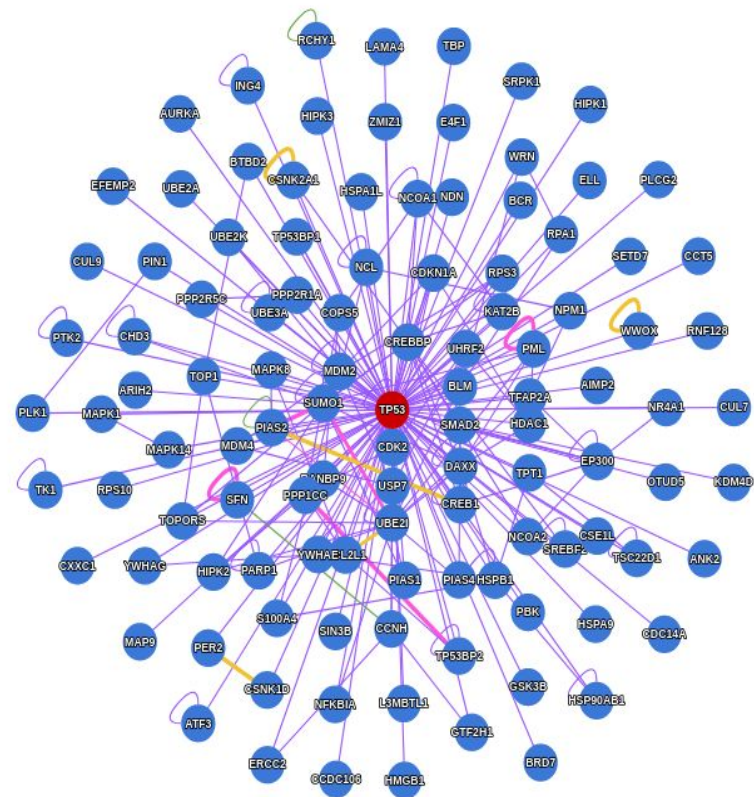


GSE19404: Gene expression analysis of primitive neuroectodermal tumors

IWO (1) X

File Edit View Tools Help Rows Columns APC ATM BMPR1A BRCA1 BRCA2 CDH24 matches 12,000 rows by 23 columns 24 rows, 0 columns selected





Differential Expression Analysis

[--- Help ---](#)

Dataset (Cancer name)

GBM

Log₂FC Cutoff:

1

Percentage Cutoff:

0.9

Differential Methods

☐ ANOVA☐ LIMMA

These two methods are used for Tumor vs Paired Normal samples.

☒ Top 10

This method are used for Tumor vs All Normal Samples.

Chromosomal Distribution

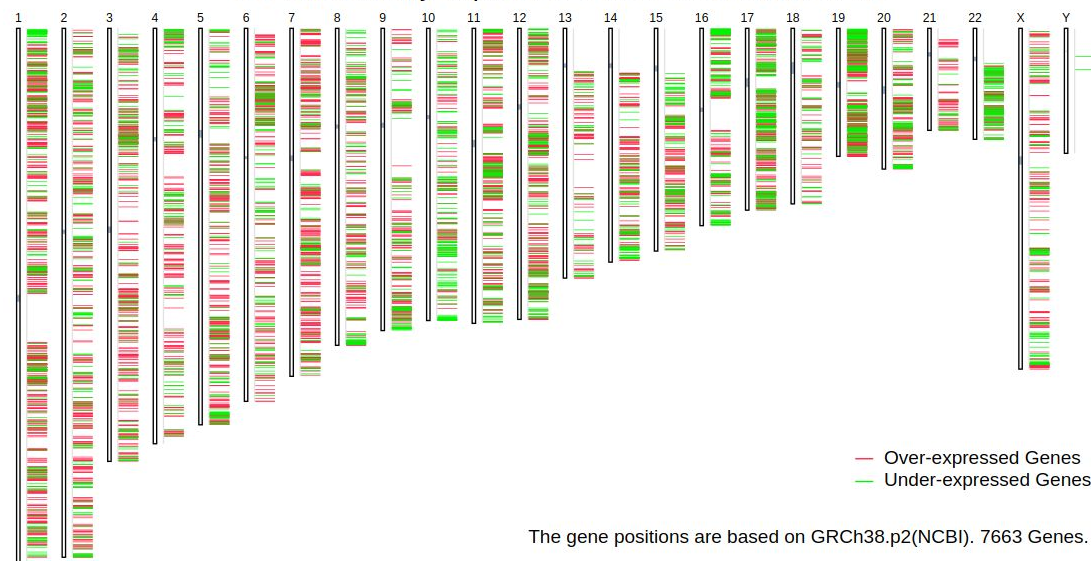
Over-expressed

Default color: Over-Red; Under-Green

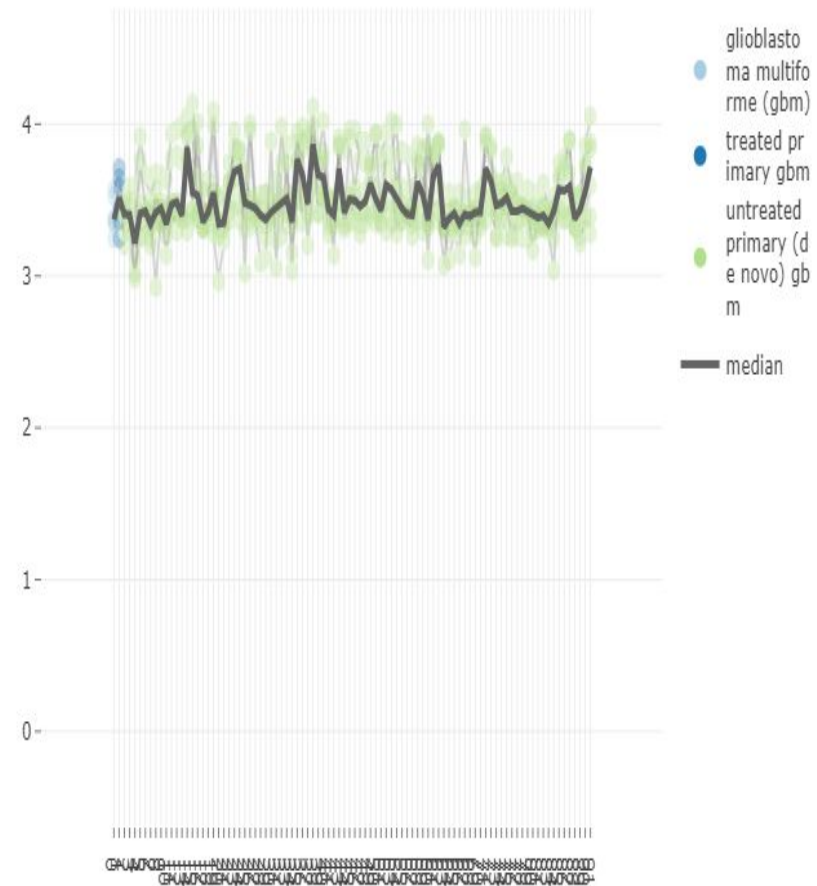
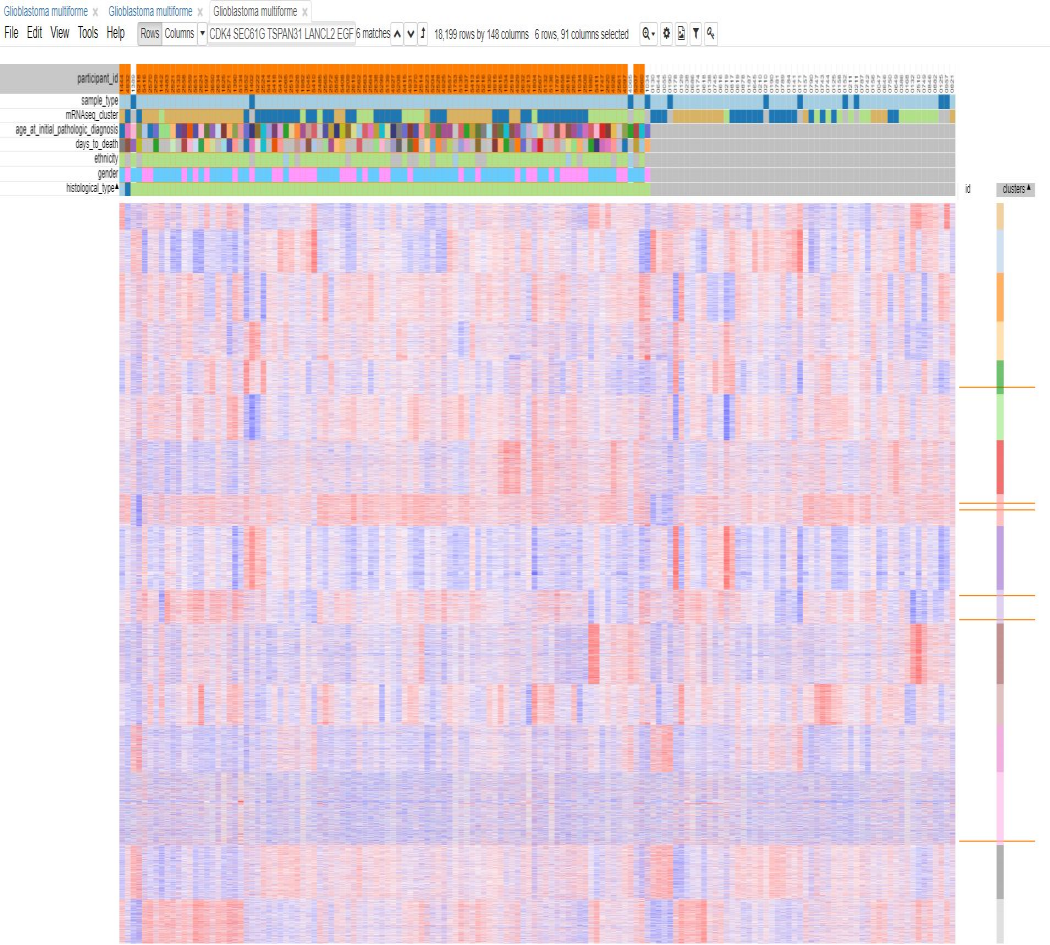
List

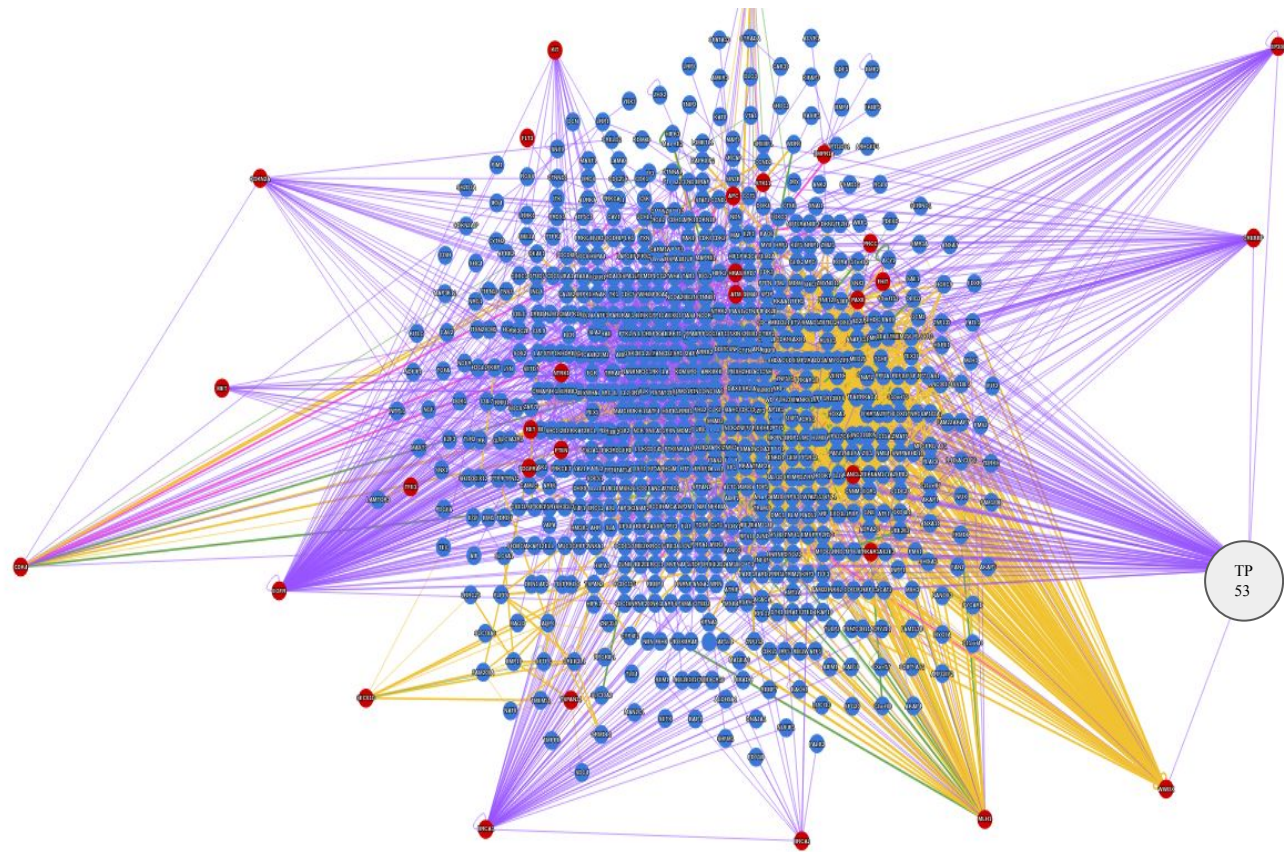
Plot

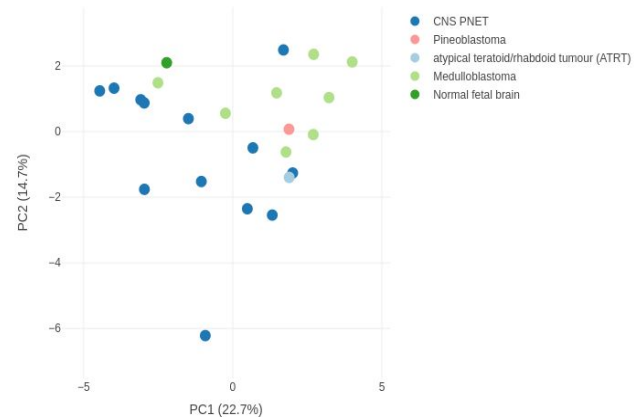
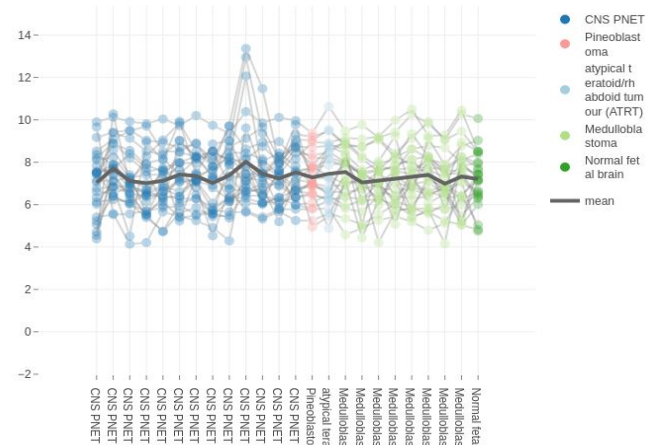
The Differentially Expressed Genes On Chromosomes



The gene positions are based on GRCh38.p2(NCBI). 7663 Genes.







Conclusion

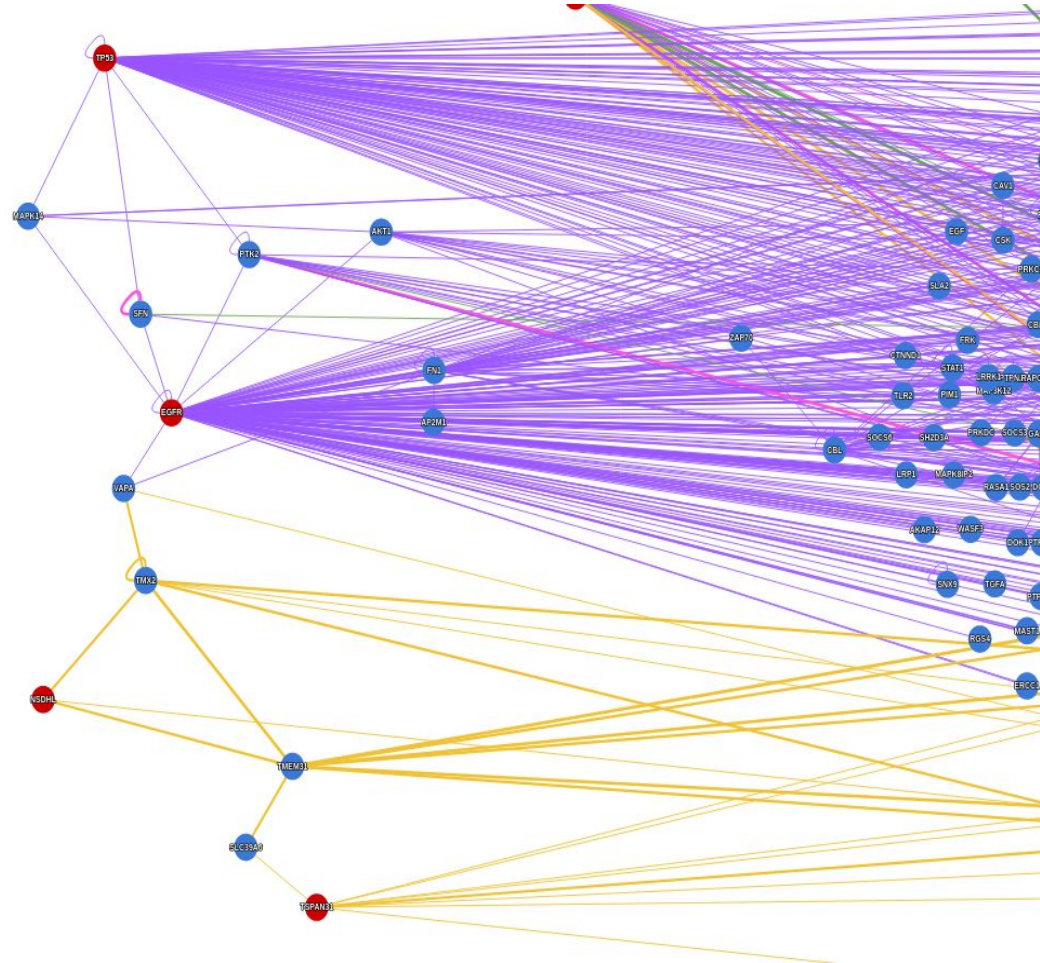
In the paper, authors identified similarities in transcriptomes of distinct human brain tumor, specifically glioblastomas of TCGA classical subtype and oligodendroglial tumors, Philips proliferative gliomas and AT/RT.

I analysed only glioblastomas for 33 genes, 14 GBM specific and remaining consensus genes from an independent study.

There have been many proposed links in literature about TP53 and its role in GBM associated genes and in general major expressed cancer genes. However, as we can see, these studies have not been validated.

The authors argued that **p53/Rb inactivation in the SVZ is relatively ineffective to generate tumors**, whereas it is **very effective when occurring during granule cell amplification in the developing cerebellum**.

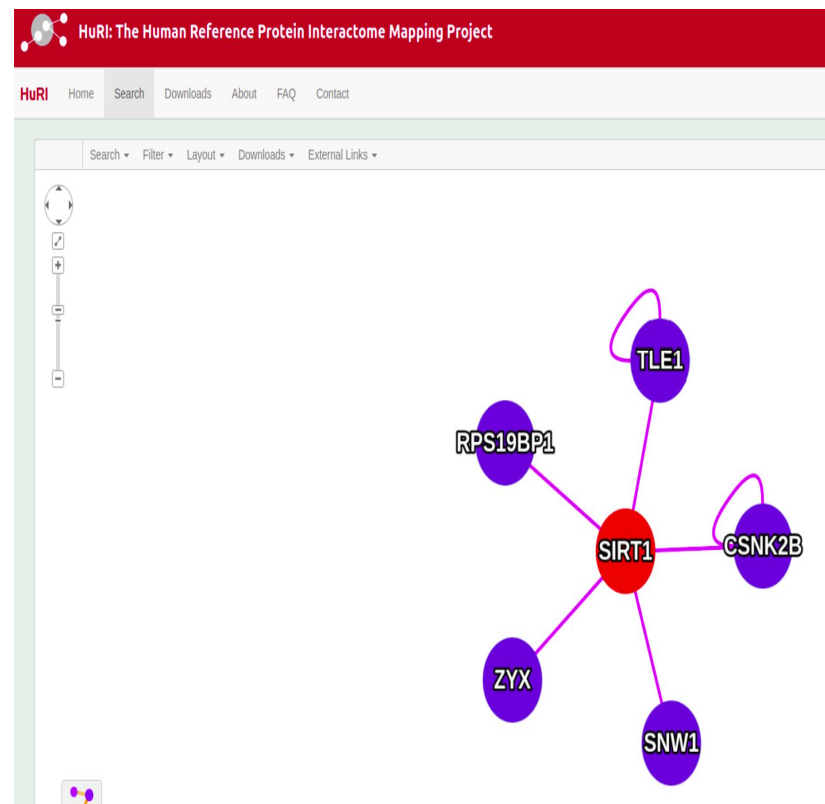
NSDHL is one such gene that is involved in granule cell amplification. If we look at TP53 and NSDHL interactome, along with over expressed genes in glioblastoma CDK4, SEC61G, TSPAN31, LANCL2, EGFR. **There are NO verified interactions yet. But a tentative connection, between TP53 and NSDHL, which links to the GBM over-expressed genes interactome.**

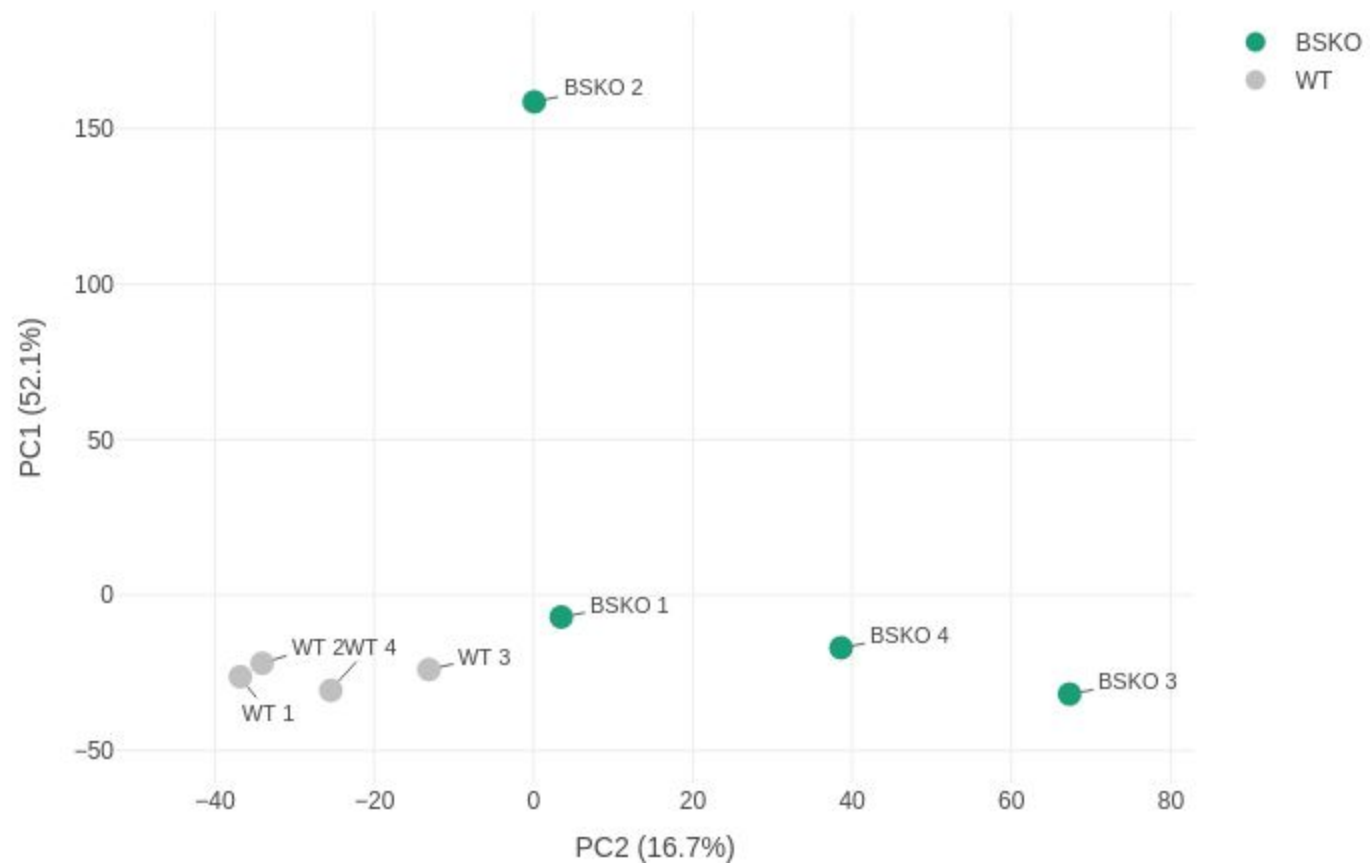


GSE28790: SIRT1 impact on global gene expression in the brain

title	BSKO 1	BSKO 3	BSKO 4	WT 1	WT 3	WT 4
geo_accession						
condition						
replicate						

id	Gene ID	Gene symbol	Mean	clusters
1422751_at	21885	Tie1	-0.14129	9.0000
1418640_at	93759	Sirt1	-0.15918	9.0000
1416728_at	13001	Csnk2b	0.00008754	4.0000
1429003_at	66354	Snw1	-0.061496	14.0000
1417240_at	22793	Zyx	0.026496	12.0000
1416034_at	12484	Cd24a	-0.10798	9.0000
1460730_at	209354	Eif2b1	-0.054672	9.0000
1429962_at	12607	Cebpz	-0.13040	9.0000
1415682_at	65246	Xpo7	-0.036930	9.0000
1453733_a_at	665503///99650	Gm7664///4933434E20Rik	-0.20071	9.0000
1415686_at	68365	Rab14	-0.084096	9.0000
1415688_at	67128	Ube2g1	-0.024962	9.0000
1415689_s_at	72739	Zkscan3	-0.073317	9.0000
1427645_a_at	60367	Il1rapl2	-0.023598	9.0000
1426238_at	12153	Bmp1	0.083489	9.0000
1426278_at	76933	Ifi272a	-0.14099	9.0000
1423082_at	67819	Derl1	-0.055009	9.0000
1451982_at	26398	Map2k4	-0.10987	9.0000
1415697_at	23881	G3bp2	-0.094279	9.0000
1415698_at	105348	Golm1	-0.0039402	9.0000
1426279_at	68152	Fam133b	-0.013249	9.0000
1420502_at	20229	Sat1	-0.21407	9.0000
1426226_at	13548	Dyrk1a	-0.31371	9.0000
1415704_a_at	321022	Cdv3	-0.054374	9.0000
1415705_at	66818	Smim7	-0.15773	9.0000
1415706_at	12847	Copa	-0.11311	9.0000
1426286_at	57753	Noc3l	-0.18089	9.0000
1426290_at	66254	Dimt1	-0.14837	9.0000
1460696_at	226527	BC026585	-0.028498	9.0000
1415710_at	231430	Cox18	-0.025671	9.0000
1415711_at	211673	Arlgef1	-0.050665	9.0000
1426221_at	67776	Vwa5a	-0.10577	9.0000
1415714_a_at	66618	Snmp27	-0.13915	9.0000
1415715_at	68366	Tmem129	-0.069134	9.0000
1426217_at	68642	Tmem216	-0.10712	9.0000
1415719_s_at	74252	Armcl	-0.053849	9.0000
1426216_at	67542	Cog6	-0.19544	9.0000
1460672_at	668661	2410002F23Rik	-0.0026872	9.0000
1426313_at	107976	Bre	-0.27315	9.0000
1415724_a_at	12540	Cdc42	-0.13168	9.0000
1415725_at	106298	Rrm3	-0.025142	9.0000
1415727_at	246703	Ana1hn	-0.041204	9.0000



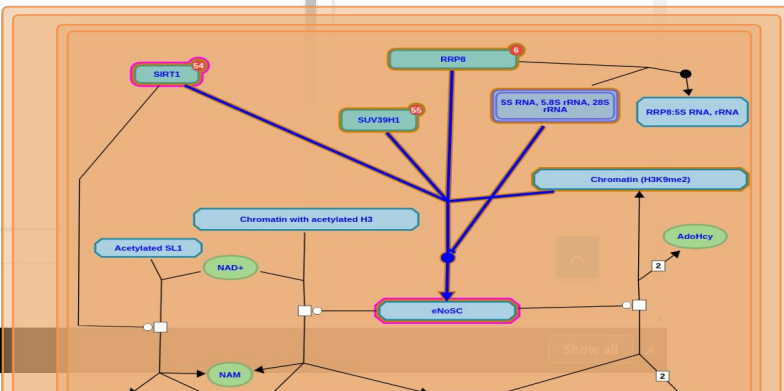
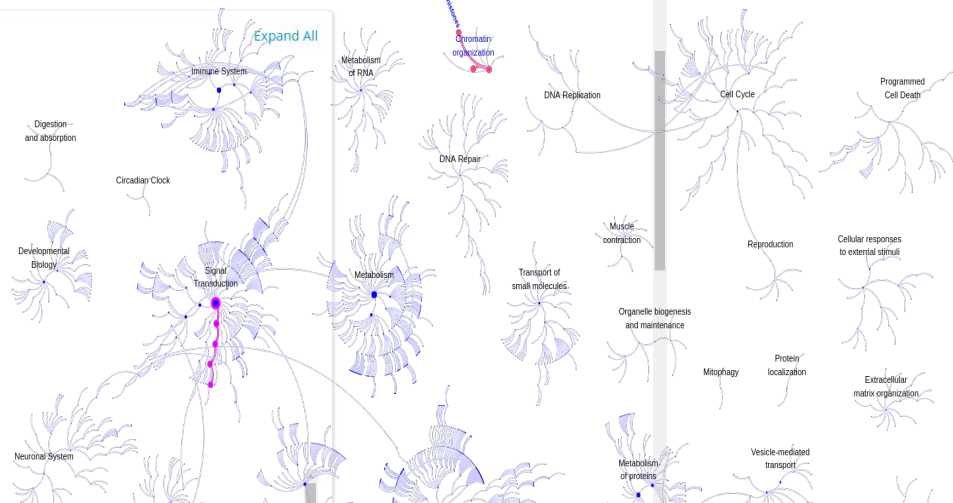


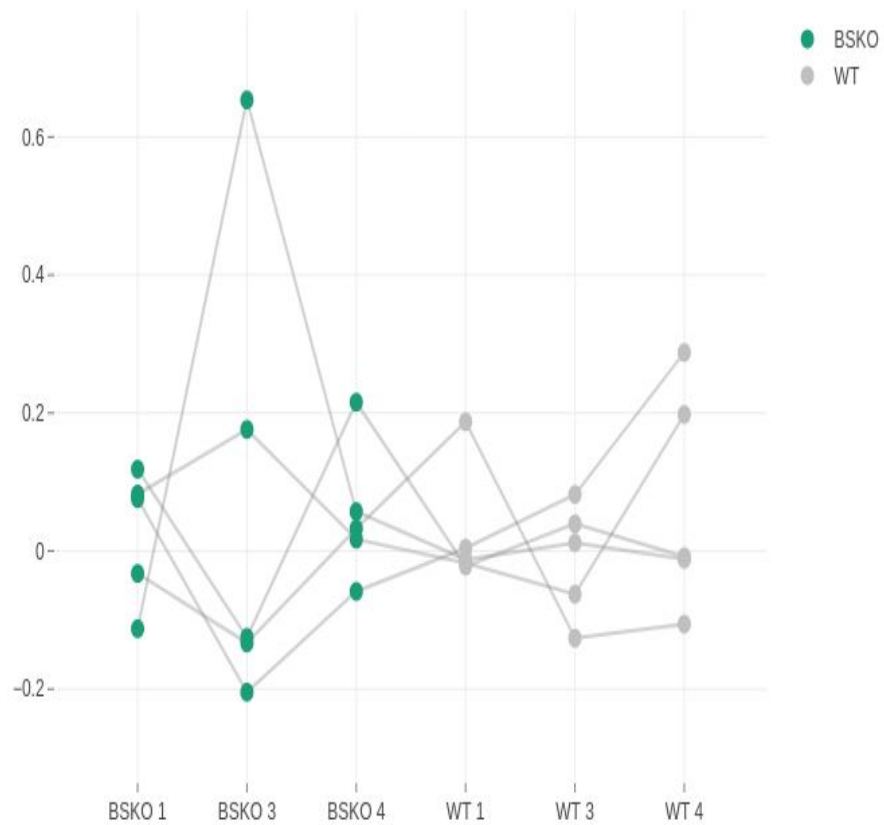
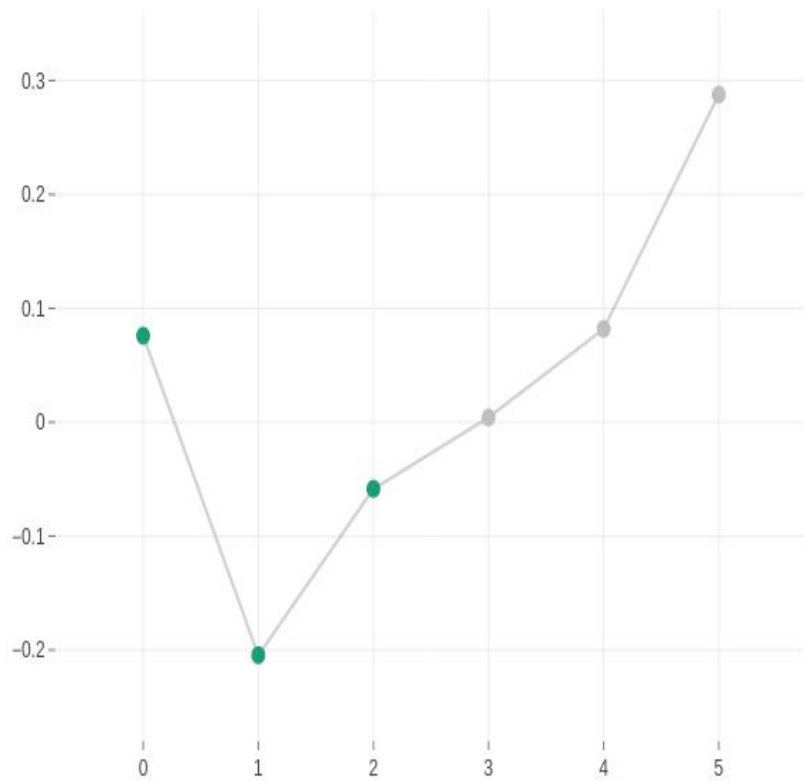
Locations in the PathwayBrowser

- Cellular responses to external stimuli (Homo sapiens)
 - Cellular responses to stress (Homo sapiens)
 - Cellular response to heat stress (Homo sapiens)
 - Regulation of HSF1-mediated heat shock response (Homo sapiens)
 - DBC1 binds SIRT1 (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - p-T454-DBC1:SIRT1 [nucleoplasm] (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - SIRT1 binds to HSF1 (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - SIRT1:HSP70:DNAJB1:AC-K80-HSF1:target gene [nucleoplasm] (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - SIRT1 deacetylates HSF1 (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - SIRT1:HSP70:DNAJB1:AC-K80-HSF1:target gene [nucleoplasm] (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
- Circadian Clock (Homo sapiens)
 - Expression of BMAL1 (ARNTL) (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - Expression of CLOCK (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
- Gene expression (Transcription) (Homo sapiens)
 - Epigenetic regulation of gene expression (Homo sapiens)
 - Negative epigenetic regulation of rRNA expression (Homo sapiens)
 - SIRT1 negatively regulates rRNA expression (Homo sapiens)
 - Formation of energy-dependent Nucleolar Silencing Complex (eNoSC) (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - eNoSC [nucleoplasm] (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - SIRT1 deacetylates TAF1B in SL1 complex (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - eNoSC deacetylates histone H3 (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - eNoSC [nucleoplasm] (Homo sapiens)
 - SIRT1 [nucleoplasm] (Homo sapiens)
 - eNoSC dimethylates histone H3 at lysine-9 (Homo sapiens)
 - eNoSC [nucleoplasm] (Homo sapiens)

External Reference Information

External Reference	UniProt:Q96EB6 SIRT1
Gene Names	SIRT1, SIRT2L1





Conclusion

SIRT1 is a NAD dependent deacetylase that provides coping mechanism against nutritional changes in cell. It is shown that by activation of genes encoding for MAO-A (monoamine oxidase). SSRIs are inhibited. SSRIs play a key role in uptake of serotonin and thus manifestation of symptoms of depression.

In analysis we can see that indeed expression of this gene is increased. Further, MAO-A inhibitors or SSRIs (selective serotonin reuptake inhibitors) normalise anxiety differences between wild-type and mutant animals.

From network analysis we can see the involvement in Sleep Cycle. Perhaps a disrupted sleep cycle and altered cell signalling response is promoting anxious behaviour in these mice.

References

Main papers:

Zenkova D, Kamenev V, Sablina R, Artyomov M, Sergushichev A. phantasmus: Visual and interactive gene expression analysis. <https://genome.ifmo.ru/phantasmus> doi: 10.18129/B9.bioc.phantasmus

Henriquez NV, Et al. n.d. “Comparative Expression Analysis Reveals Lineage Relationships between Human and Murine Gliomas and a Dominance of Glial Signatures during Tumor Pro... - PubMed - NCBI.” Accessed February 15, 2019. <https://www.ncbi.nlm.nih.gov/pubmed/23887970>.

Libert, Sergiy, Kelli Pointer, Eric L. Bell, Abhirup Das, Dena E. Cohen, John M. Asara, Karen Kapur, et al. 2011. “SIRT1 Activates MAO-A in the Brain to Mediate Anxiety and Exploratory Drive.” *Cell* 147 (7): 1459–72.

Lu, Tao, Liviu Aron, Joseph Zullo, Ying Pan, Haeyoung Kim, Yiwen Chen, Tun-Hsiang Yang, et al. 2014. “REST and Stress Resistance in Ageing and Alzheimer’s Disease.” *Nature* 507 (7493): 448–54.

Additional:

Futreal, P. Andrew, P. Andrew Futreal, Lachlan Coin, Mhairi Marshall, Thomas Down, Timothy Hubbard, Richard Wooster, Nazneen Rahman, and Michael R. Stratton. 2004. “A Census of Human Cancer Genes.” *Nature Reviews. Cancer* 4 (3): 177–83.

HuRI, GEPIA, Reactome, Allen Brain Reference Atlas and RNAseq dataset explorer, TCGA