Neurogenomics

By Dhruv Reddy Patel

NeuroGenomics

-The study of how the genome as a whole contributes to the evolution, development, structure and function of the nervous system.

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Early Origins

- The human genome project
- Widely-available databases of genomes- mRNAs and ESTs
- Functional genomics, e.g. microarrays
- Knockout and transgenic mice

The word “ALL”

- What are all the mRNAs/proteins in a particular cell?
- What are all the components of the human nervous system?
- What are all the types of neurons in the brain?
- What are all the effects of an antagonist on a specific neuron?

This enables the unprecedented power of genomics to

understand fundamental biology and uncover causes of

specific diseases.

Early skepticism of human genomics- Shut down by prominent results.

EST database (early application of web for biology)

Large-scale transcript map of human genome

Comparative genomics (different species)

SNPs (Single Nucleotide Polymorphisms) for genome-wide association studies

Problems of Neurogenomics

– The nervous system has anatomic structure important for development, function, specificity

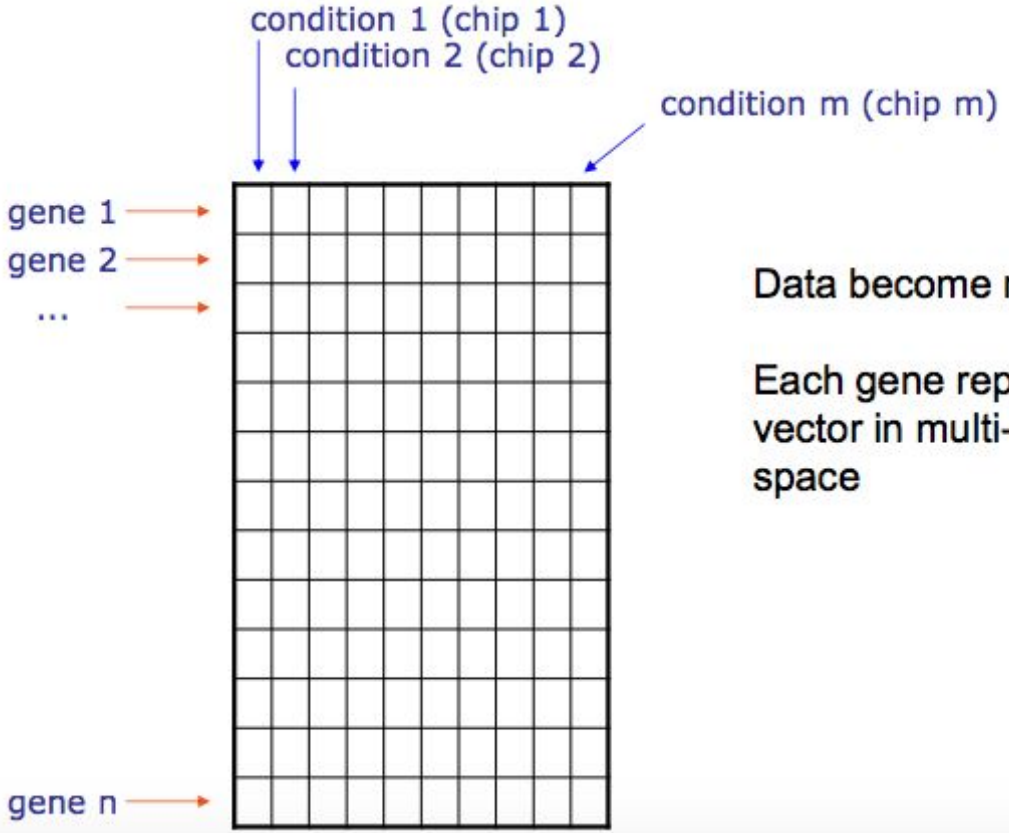
– Hard to scale up to apply genomics to anatomy (ISH, GENSAT)

– Mis-use or over-use of high-throughput technologies

Different experiments and methods of analysis in Neurogenomics

- Microarray (Experiment Matrix)
- Hierarchical Clustering
- Logs are used
- Volcano Plot

Microarray: experiment matrix



Data become matrix

Each gene represented by a vector in multi-dimensional space

Hierarchical clustering

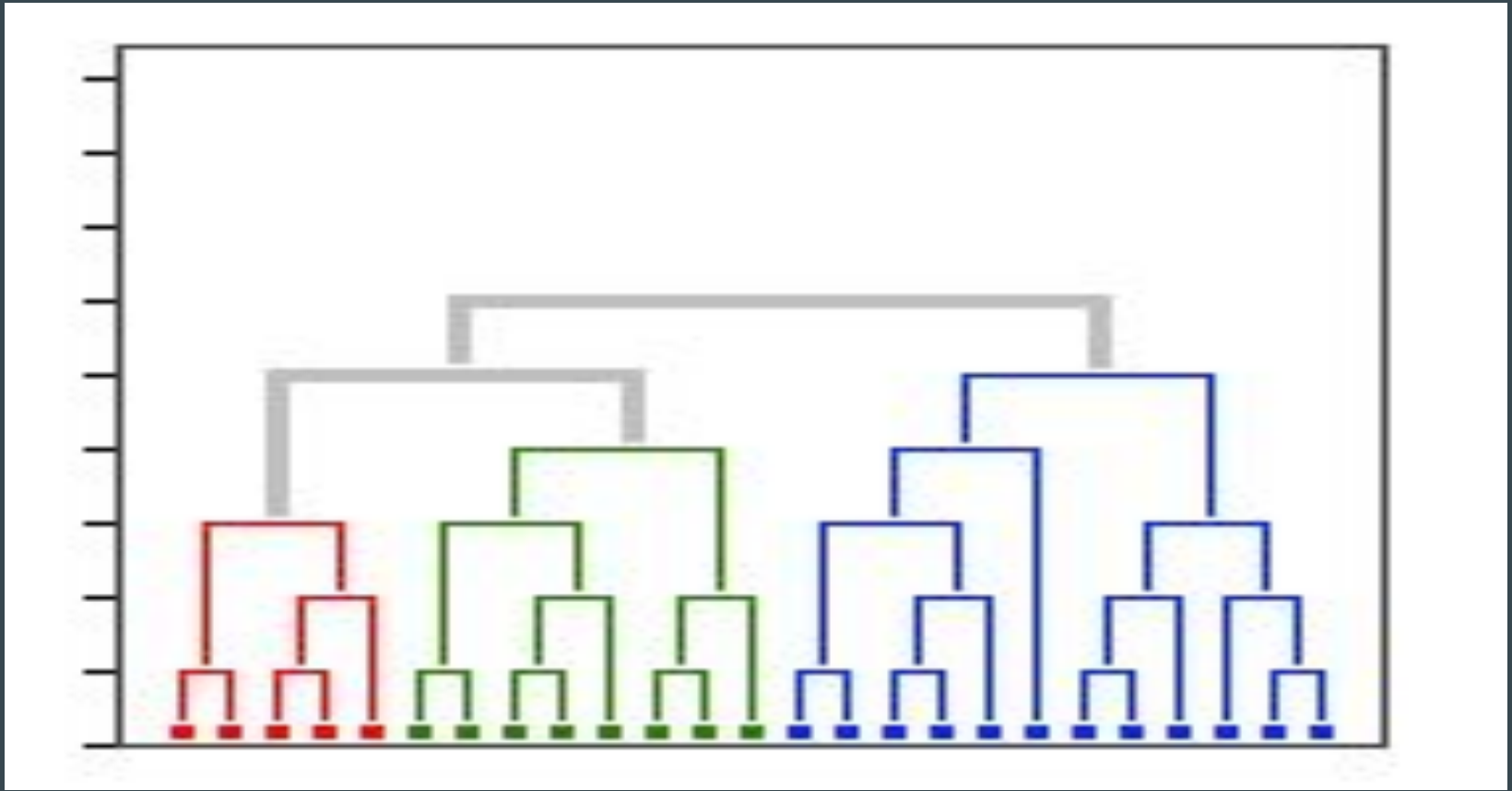
Measures

1. Single linkage
2. Average linkage
3. Complete linkage

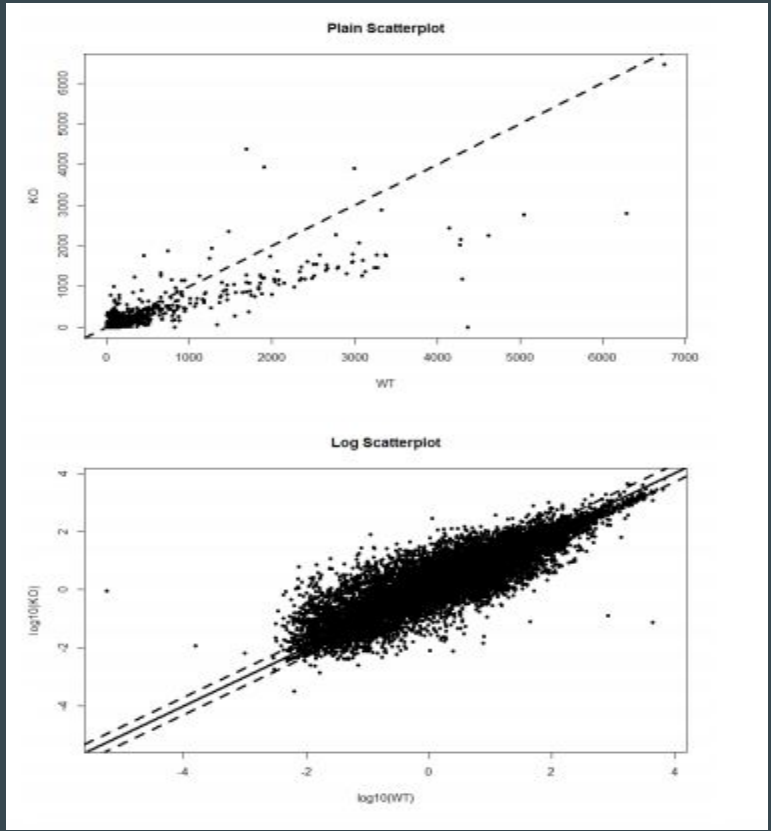
Different types of Distances

1. Euclidean
2. Correlation distance

Hierarchical clustering

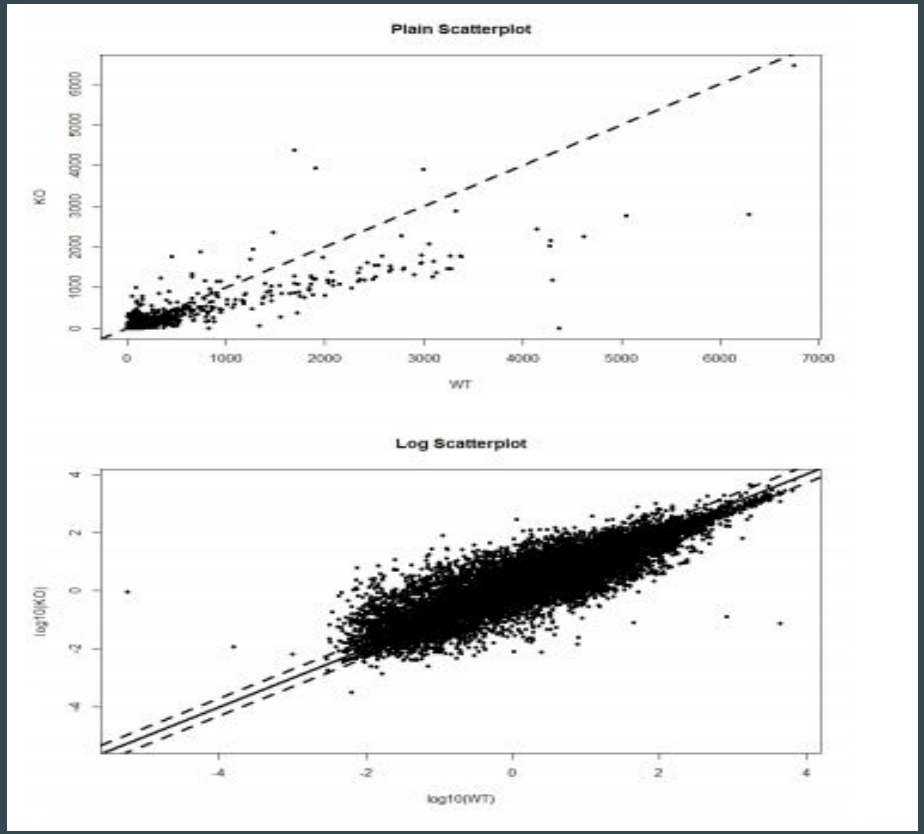


Logs method of research is used in NeuroGenomics



Logs method of research is used in NeuroGenomics

Using log of intensity allows visualization of a broader range of signal in a more uniformly-spaced manner.



Volcano Plot

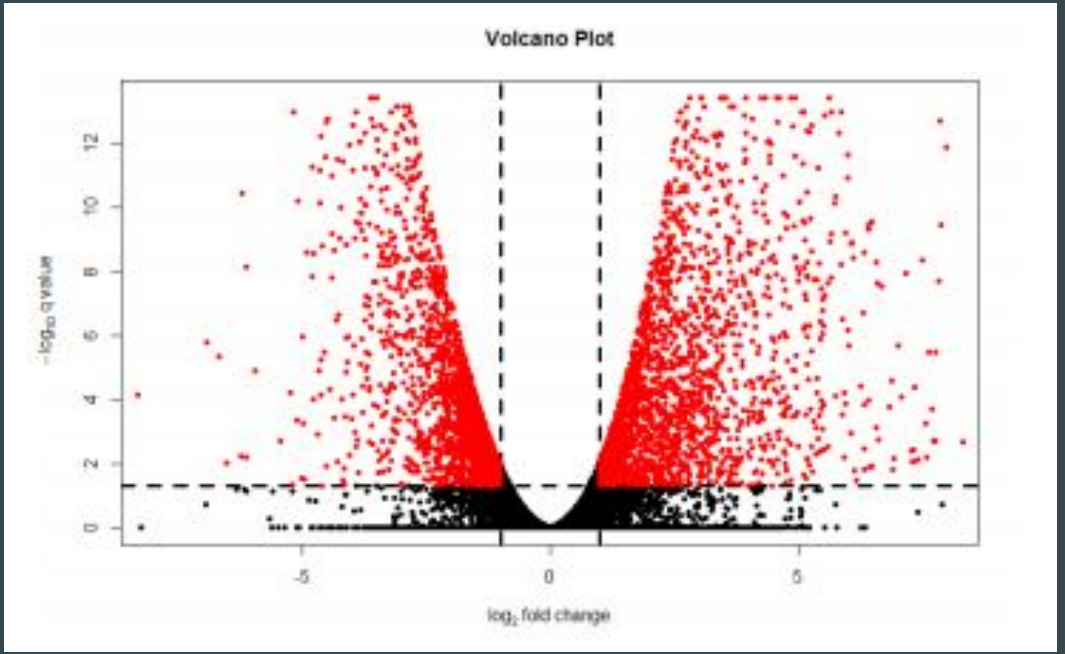
– Vertical lines are

2-fold cut-offs

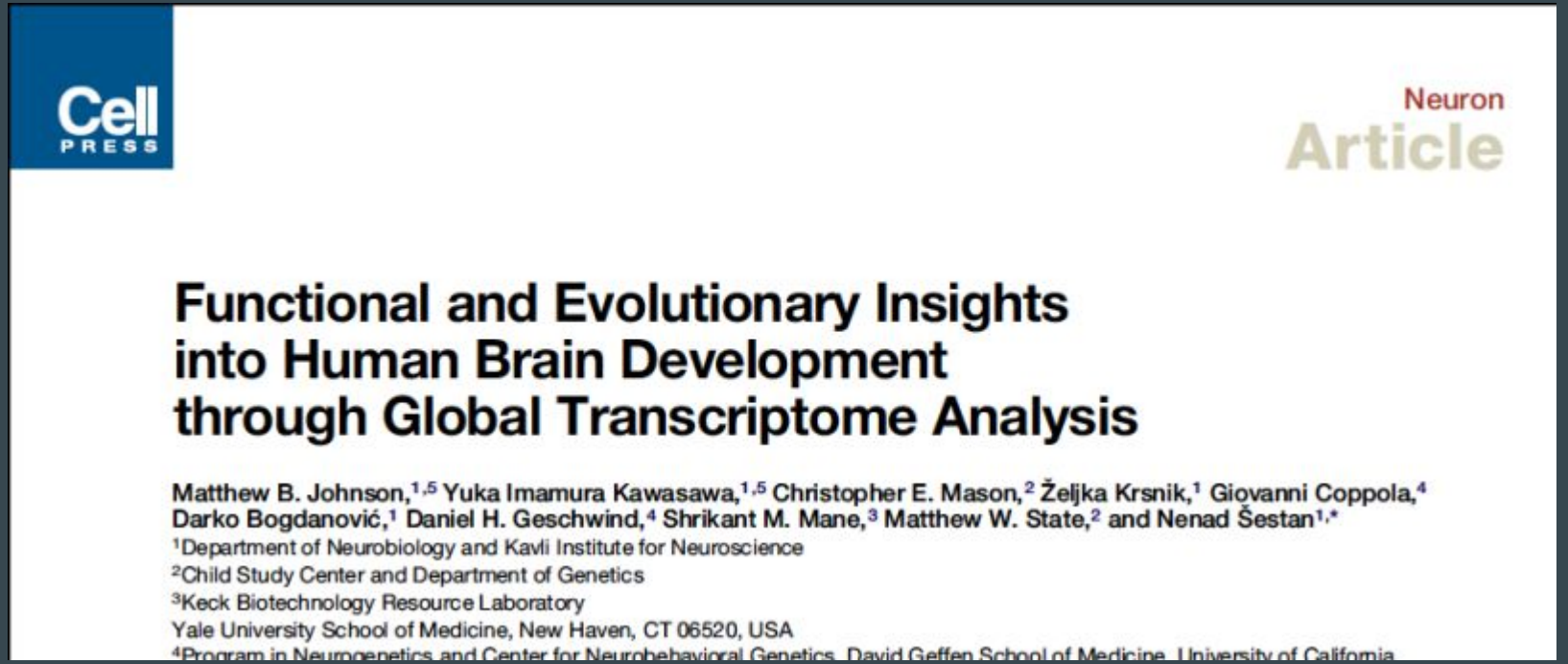
– Red dots show genes with

at least 2-fold change

AND $p \leq 0.05$.



Human brain development



Cell PRESS

Neuron

Article

Functional and Evolutionary Insights into Human Brain Development through Global Transcriptome Analysis

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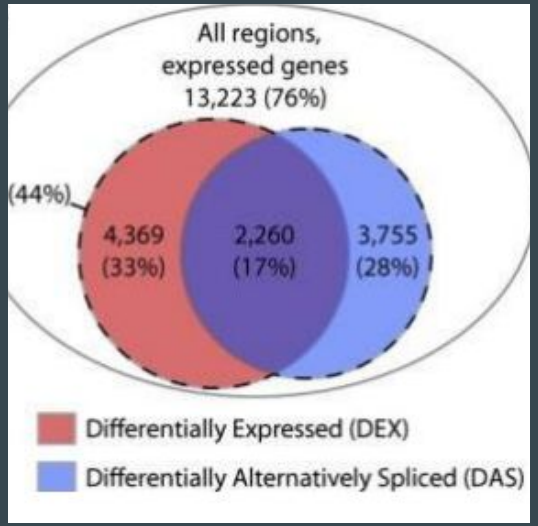
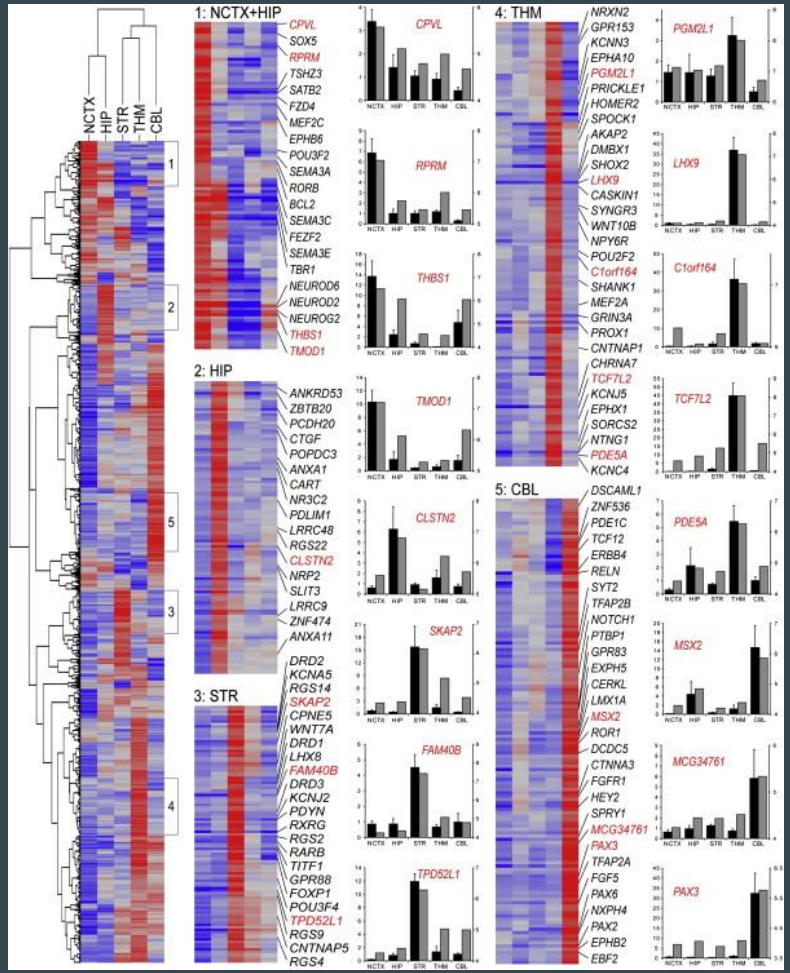
Analysis of data/results

13,223/17,421 genes were detected which is more than 3/4ths of the genes.

33% of those were differentially expressed

Of those 13,223, a little more than 25% had differential exon usage patterns.

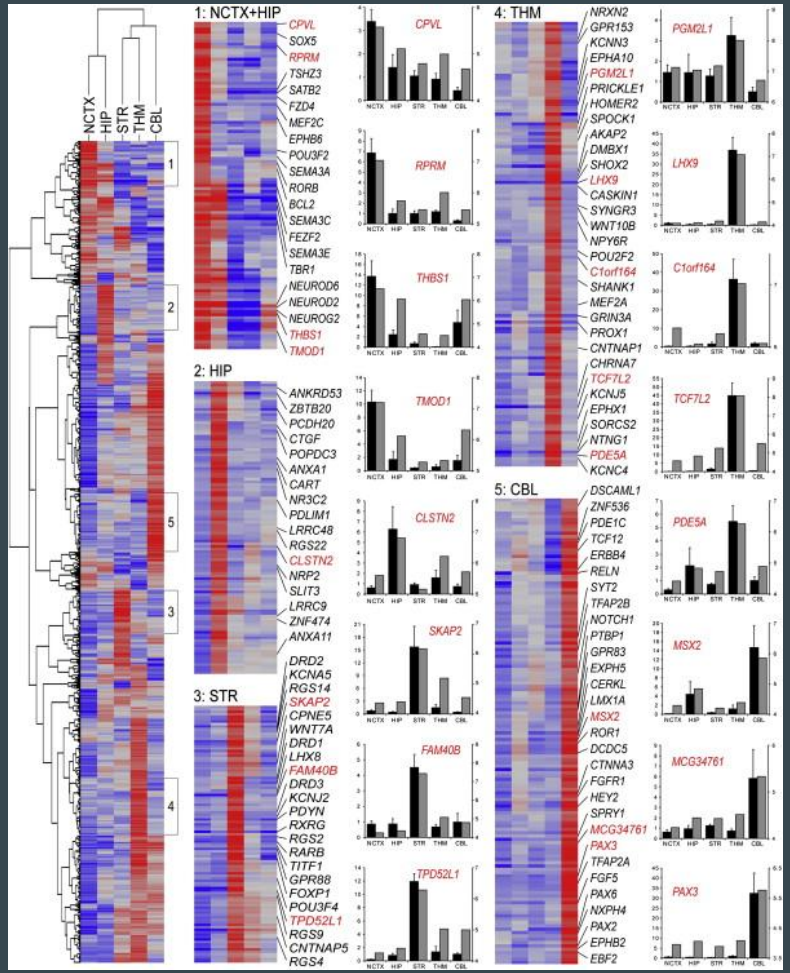



NCTX
HIP
STR
THM
CBL
1
2
5
3
4
1: NCTX+HIP
CPVL
SOX5
RPRM
TSHZ3
SATB2
FZD4
MEF2C
EPHB6
POU3F2
SEMA3A
RORB
BCL2
SEMA3C
FEZF2
SEMA3E
TBR1
NEUROD6
NEUROD2
NEUROG2
THBS1
TMOD1
2: HIP
ANKRD53
ZBTB20
PCDH20
CTGF
POPDC3
ANXA1
CART
NR3C2
PDLIM1
LRRC48
RGS22
CLSTN2
NRP2
SLIT3
LRRC9
ZNF474
ANXA11
3: STR
DRD2
KCNA5
RGS14
SKAP2
CPNE5
WNT7A
DRD1
LHX8
FAM40B
DRD3
KCNJ2
PDYN
RXRG
RGS2
RARB
TITF1
GPR88
FOXP1
POU3F4
TPD52L1
RGS9
CNTNAP5
RGS4
4: THM
NRXN2
GPR153
KCNN3
EPHA10
PGM2L1
PRICKLE1
HOMER2
SPOCK1
AKAP2
DMBX1
SHOX2
LHX9
CASKIN1
SYNGR3
WNT10B
NPY6R
POU2F2
C1orf164
SHANK1
MEF2A
GRIN3A
PROX1
CNTNAP1
CHRNA7
TCF7L2
KCNJ5
EPHX1
SORCS2
NTNG1
PDE5A
KCNC4
5: CBL
DSCAML1
ZNF536
PDE1C
TCF12
ERBB4
RELN
SYT2
TFAP2B
NOTCH1
PTBP1
GPR83
EXPH5
CERKL
LMX1A
MSX2
ROR1
DCDC5
CTNNA3
FGFR1
HEY2
SPRY1
MCG34761
PAX3
TFAP2A
FGF5
PAX6
NXPH4
PAX2
EPHB2
EBF2
CPVL
RPRM
THBS1
TMOD1
CLSTN2
SKAP2
FAM40B
TPD52L1
PGM2L1
LHX9
C1orf164
TCF7L2
PDE5A
MSX2
MCG34761
PAX3
NCTX HIP STR THM CBL

Hierarchical clustering

Which of these are the most similar?

- Look at the ones with the least difference in the bar graphs.



Human Brain Development (2009)

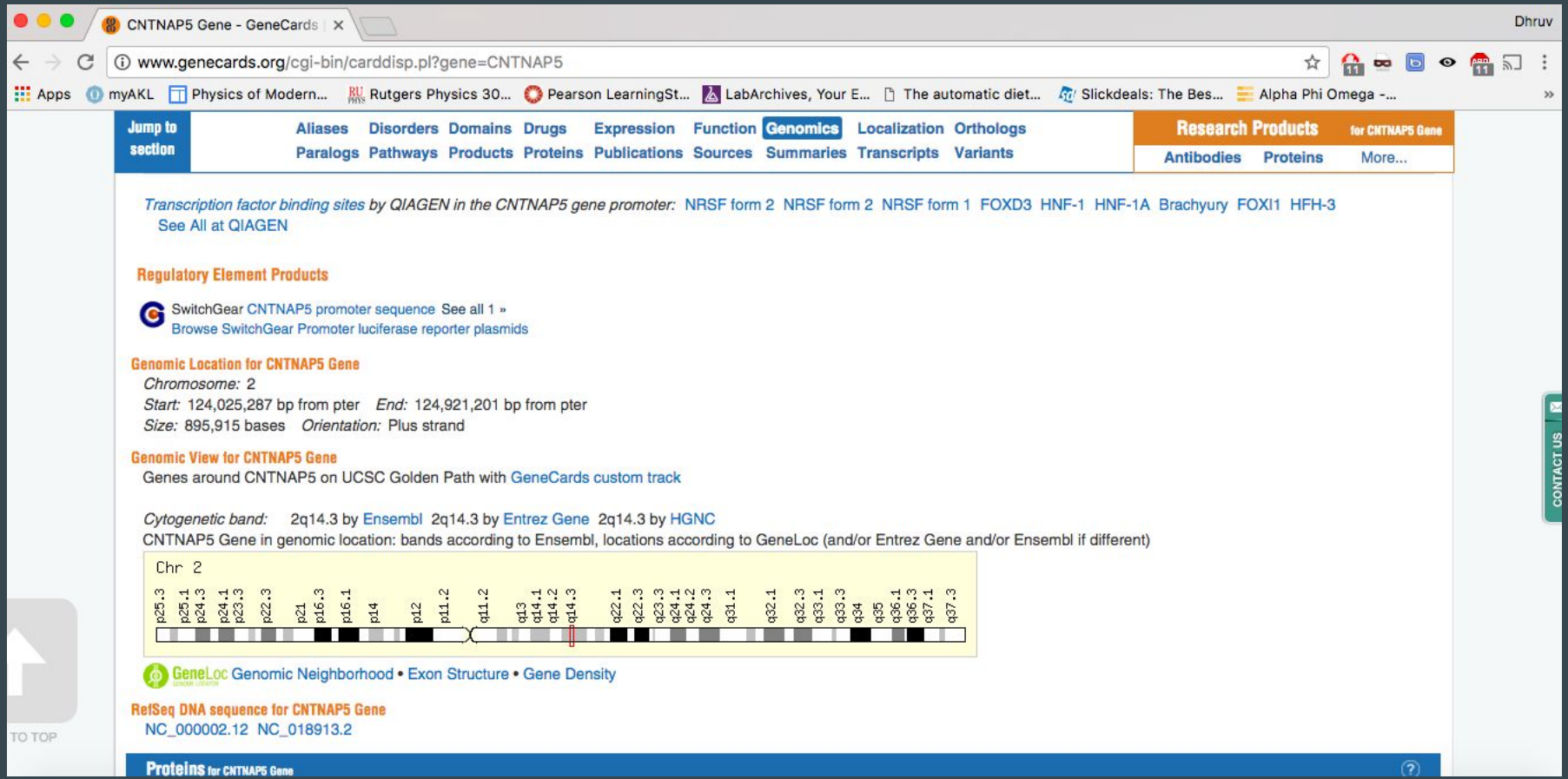
Human brain development is different than rodents mainly due to alternative splicing.

Paper states that mid-gestation is the key step in brain development. There are expected to be more differences between regions (especially in the frontal cortex) due to the obviously more complex developmental program that humans have.

It is found that some gene expression differences are due to alternative splicing or alternative cap site or alternative polyA site usage.

They also found that NeuroD2, NeuroD6, and Neurog2 and attempt to associate that with neurogenesis.

Led to the CNTNAP5 gene



Similar but different?

CNTNAP2 disruption was associated with speech delay and autism.

Deletions of CNTNAP5 associated with autism spectrum disorders (ASD) and dyslexia.

This was different from the CNTNAP5 gene but this means that they’re in the same gene family.

Concluded that CNTNAP5 is member of neurexin family. (Important in maintaing synapses)

Intragenic CNTNAP2 Deletions: A Bridge Too Far, Poot M. Published: February 10. (2017).

According to a paper (Poot 2017), deletions of both CNTNAP2 alleles produced truncated proteins lacking the transmembrane or some of the extracellular domains, or no protein at all.

Truncated- shortened or cut off.

Questions answered

A study (Prabhakar 2006) asked which of these most different in human, thought to be evolutionarily recent (human accelerated or HA-CNS).

Therefore, there is a correlation between the alternatively spliced regions across various regions of the brain in different species and higher level cognition.

It was then found that mutations in Human Accelerated Regions Disrupt Cognition and Social Behavior.

Further research

Now, it is important to find out which genes are absolutely essential for normal development of speech and cognition.

This refers to the Higher order of genes essential for humans.

References

Intragenic CNTNAP2 Deletions: A Bridge Too Far, Poot M. Published: February 10. (2017).

Functional and Evolutionary Insights into Human Brain Development through Global Transcriptome Analysis Matthew B. Johnson et al. (2009)

Transcriptional Regulation and Alternative Splicing Make for Better Brains Colette Dehay and Henry Kennedy (2009)

Accelerated Evolution of Conserved Noncoding Sequences in Humans. Shyam Prabhakar (2006)

Mutations in Human Accelerated Regions Disrupt Cognition and Social Behavior Ryan N. Doan1, Byoung-Il Bae1 et al. (2016)