Gene Expression Analysis

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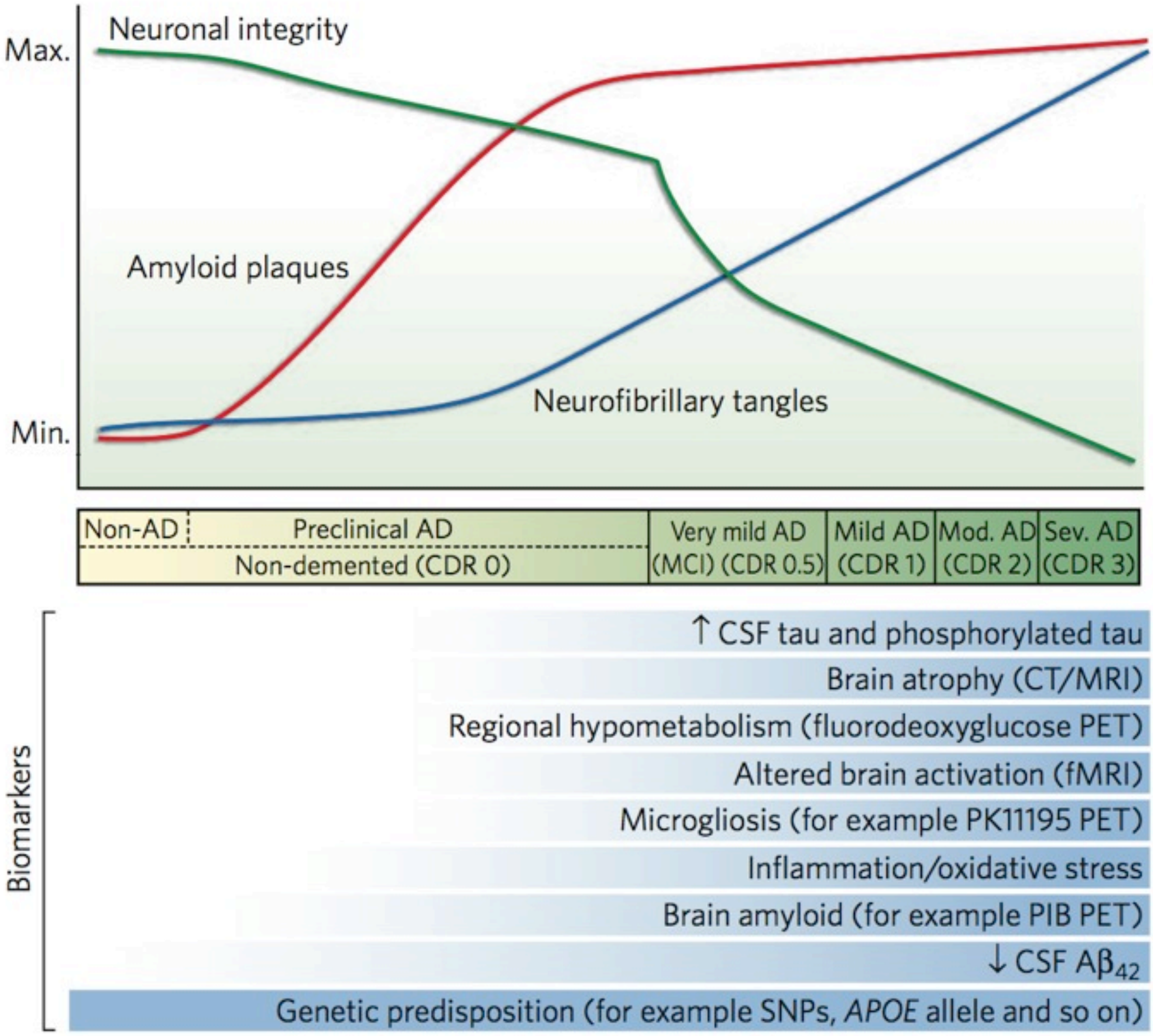
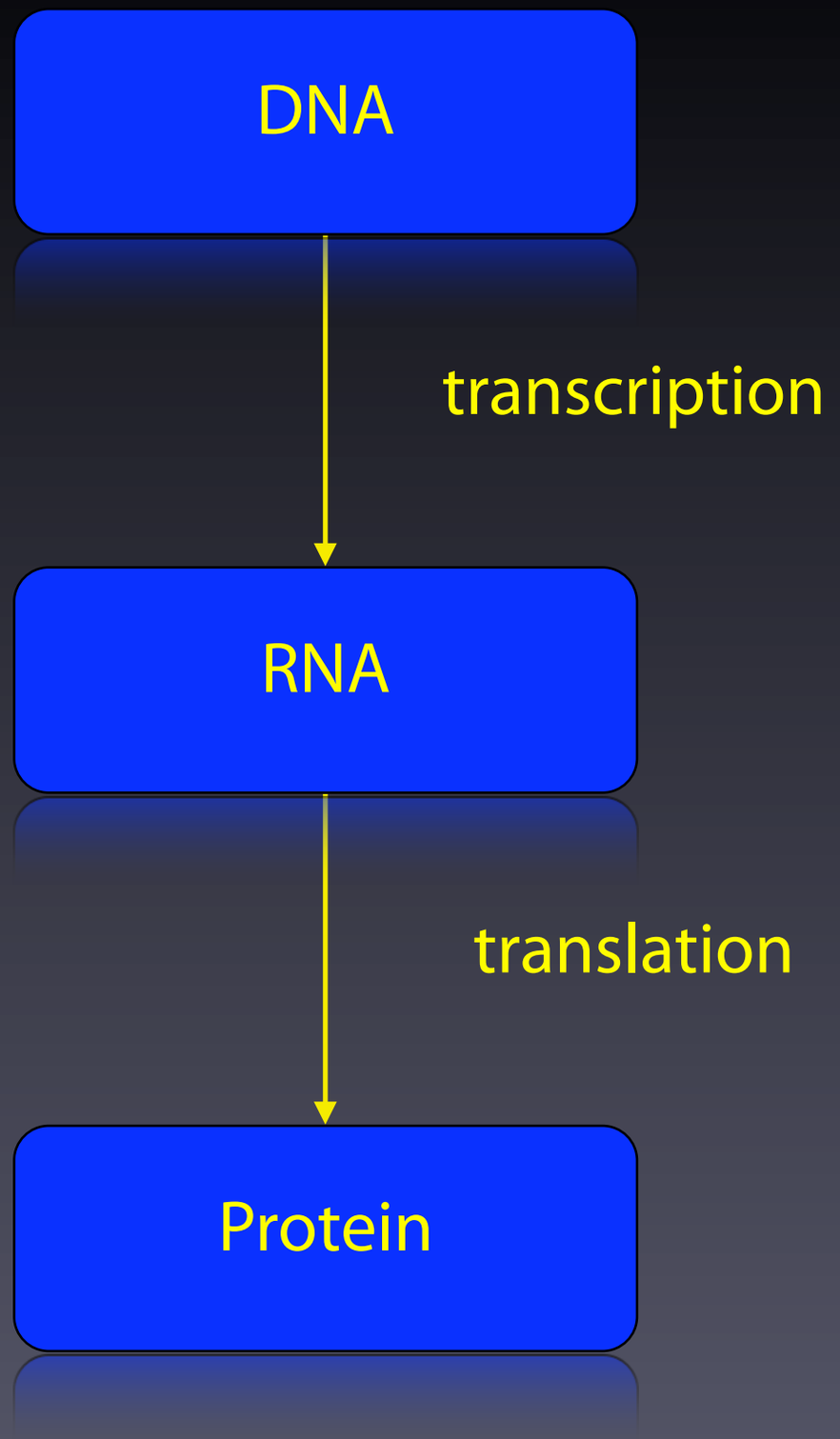
Department of Neurology

Biomarkers in Dementia?

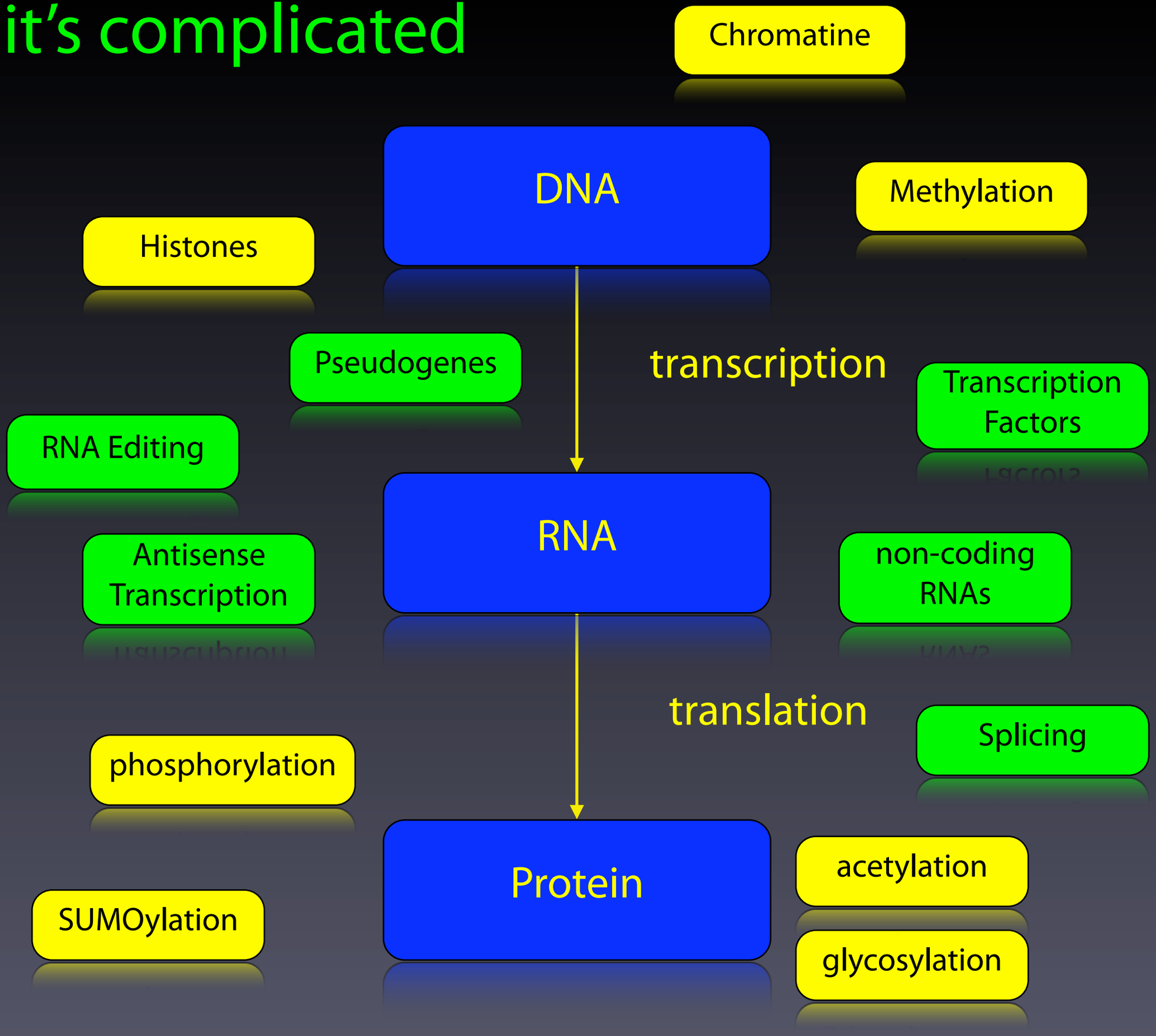


Perrin, Fagan & Holtzman, Nature 2009

it's simple...



...and it's complicated



Biomarkers in AD?

SITE POLL ARCHIVE

Important Notice: Opine Online provides an informal way for the research community to express its views on current topics. The results are not a scientific poll and do not necessarily reflect the percentages of all Alzheimer researchers who agree with these positions.

January 2010

Poll Question: What method will be routinely used to predict AD risk?

Neuroimaging
9
Psychometrics
3
Genetics
4
CSF biomarkers
7
Plasma biomarkers
9
A combination of the above
35
Ouija board
1
Other
4

Responses: 72

www.alzforum.org

Towards a Personalized Genetic Risk Map

Non-Genetic Factors

APOE

CLU

PICALM

SORL1

common variant

MAPT A152T

Rare variant

Rare variant

Rare variant

Rare variant

Rare variant

Rare variant

Gene Expression

Epigenetics

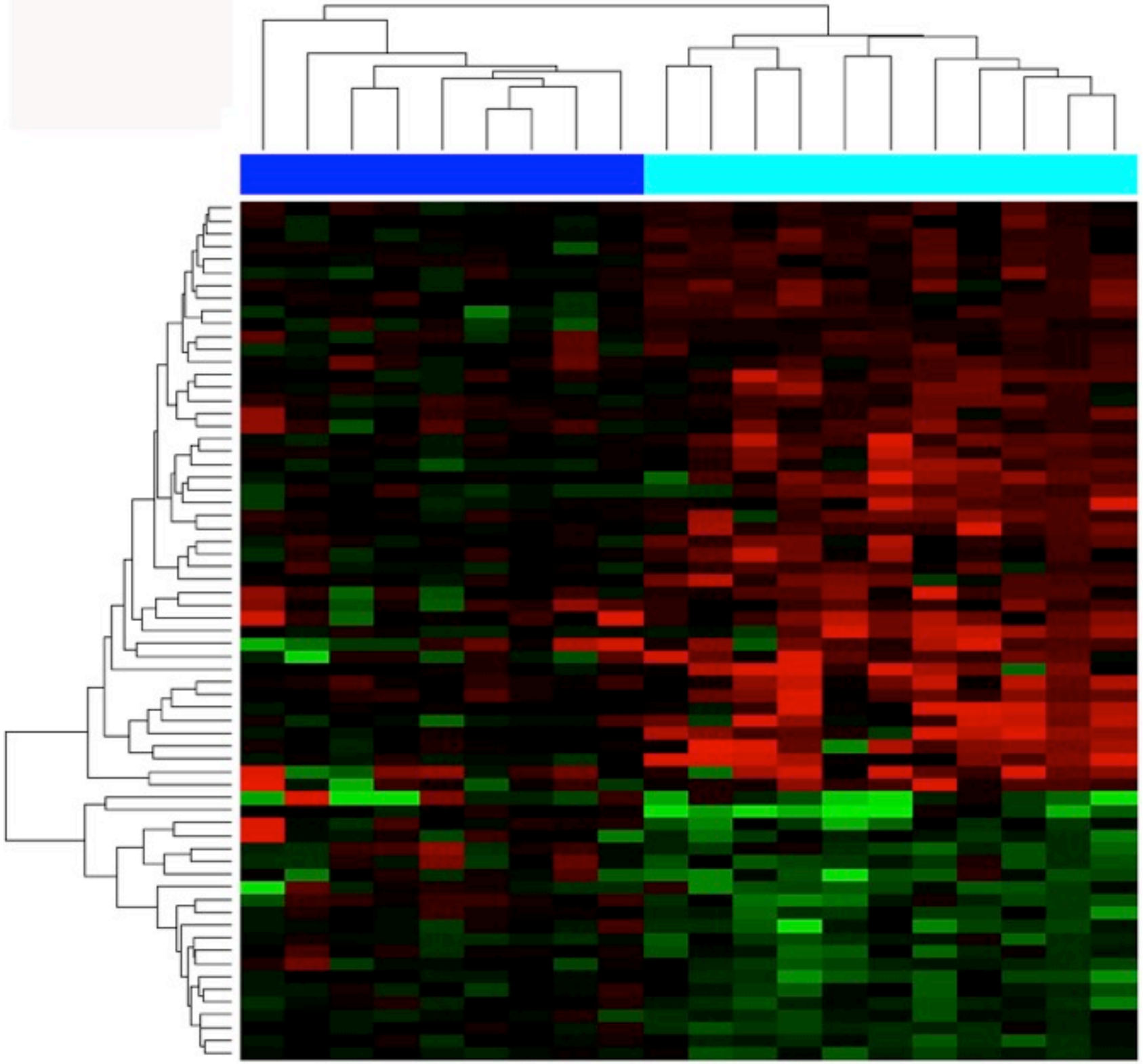
Imaging early features

Raw Data

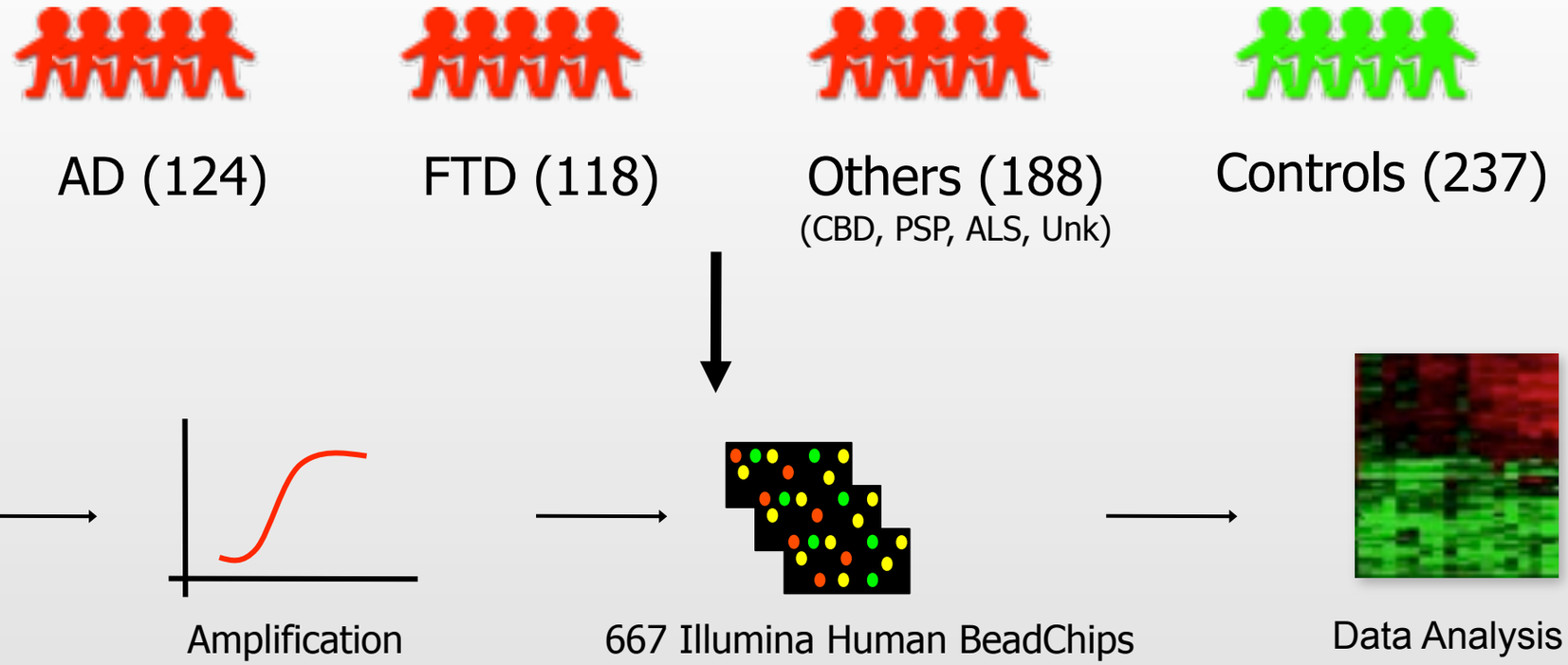
IlluminaExample.xls

	A	B	C	D	E	F	G	H	I	J
1	PROBE_ID	SYMBOL	A.AVG_Signal	A.Detection Pval	A.BEAD_STDERR	A.Avg_NBEADS	B.AVG_Signal	B.Detection Pval	B.BEAD_STDERR	B.Avg_NBEADS
2	ILMN_205527	A1BG	157.385	0.126506	10.93545	33	175.4265	0.09789157	9.758943	34
3	ILMN_181431	A2BP1	112.0078	0.936747	4.296019	37	119.7849	0.7454819	4.683157	35
4	ILMN_235916	A2BP1	112.5929	0.9262048	5.775262	40	110.989	0.9096386	4.557829	38
5	ILMN_173150	A2BP1	126.7409	0.5527108	6.105692	42	142.0882	0.2966867	6.688594	37
6	ILMN_178768	A2BP1	171.4069	0.07228915	9.987462	33	163.22	0.1475904	10.81884	32
7	ILMN_174560	A2M	117.1712	0.8268072	5.335636	37	121.8938	0.6972892	4.778038	49
8	ILMN_213649	A2ML1	109.5976	0.9608434	5.266454	44	118.7674	0.7635542	8.207358	24
9	ILMN_166811	A3GALT2	125.9102	0.5888554	6.676357	35	118.8123	0.7620482	5.315169	35
10	ILMN_229555	A3GALT2	129.9492	0.4518072	6.132965	40	112.2986	0.8870482	3.990057	40
11	ILMN_173504	A4GALT	132.6967	0.4036145	6.300234	42	118.4671	0.7710843	4.641597	42
12	ILMN_168075	A4GNT	181.5576	0.04518072	9.307973	24	163.6213	0.1415663	9.414104	30
13	ILMN_237518	AAA1	136.2968	0.3343374	7.173608	44	123.0318	0.6762048	5.835261	39
14	ILMN_165945	AAA1	135.9789	0.3388554	6.565996	39	139.3544	0.3298193	5.865483	39
15	ILMN_176738	AAA1	124.4308	0.6159639	4.977392	30	146.6352	0.2454819	7.951816	29

Data Visualization: Heatmap



Molecular Classification in Dementia



Aims of the Study

Low-Hanging Fruit

To Look at the Expression Levels of Specific Genes of Interest

~~**Within Region**~~

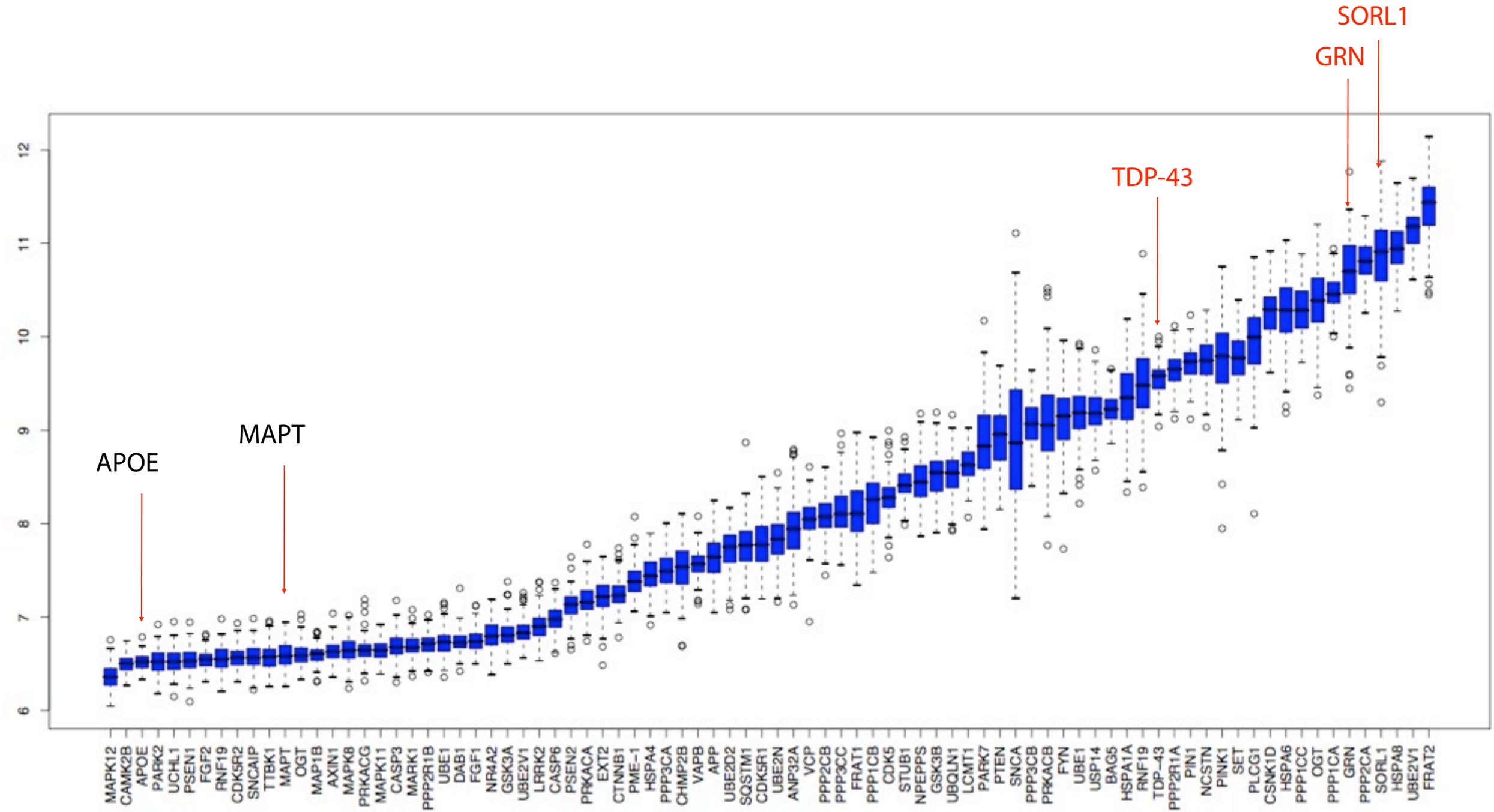
~~To Look for Differentially Expressed Genes in AD vs. FTD~~

Ambitious (Delusional)

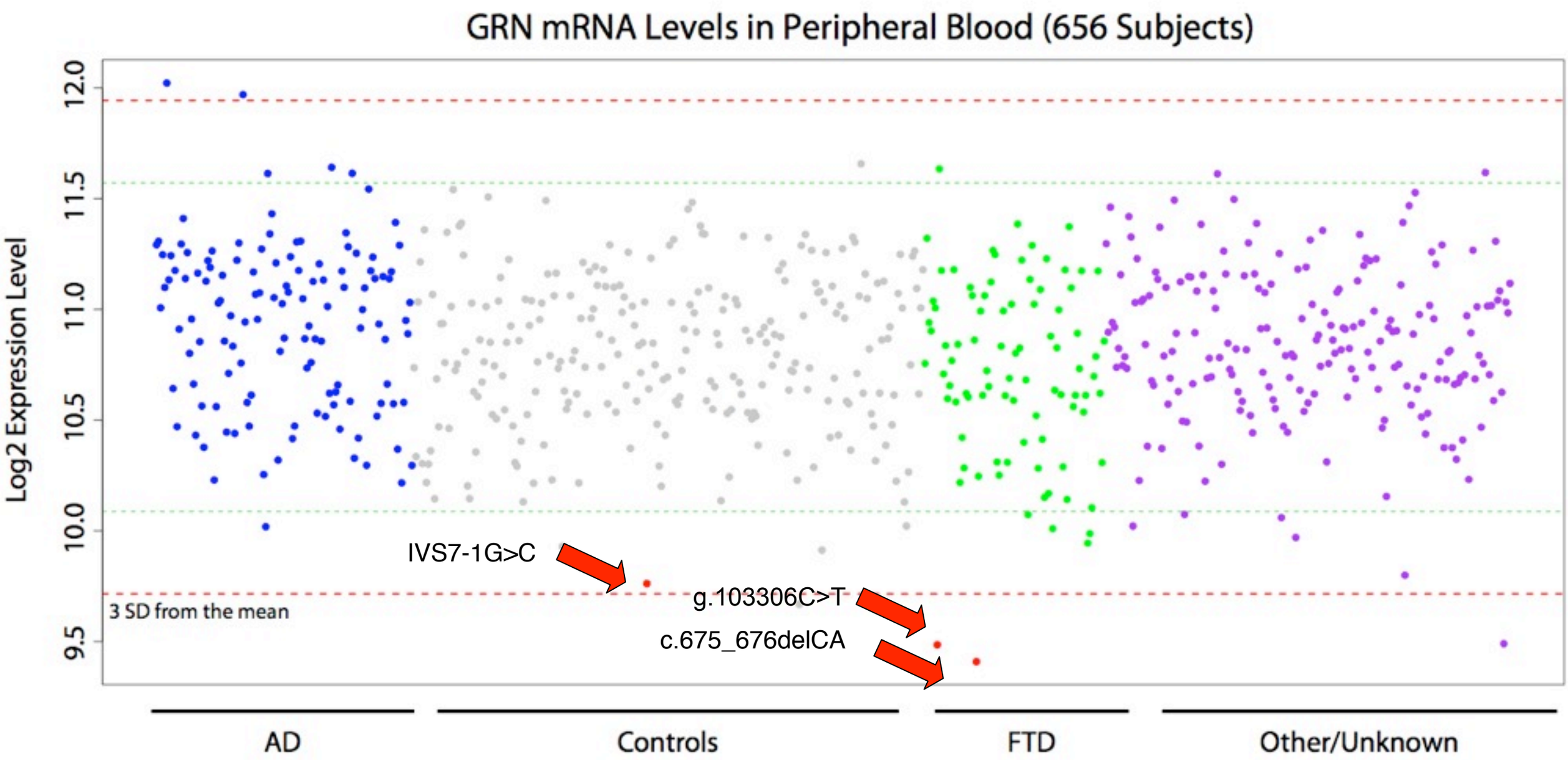
To Build a Molecular Classifier Based On Gene Expression Data

Blood vs. Brain

Peripheral Blood Expression Levels of 81 Neurodegeneration-Related Genes

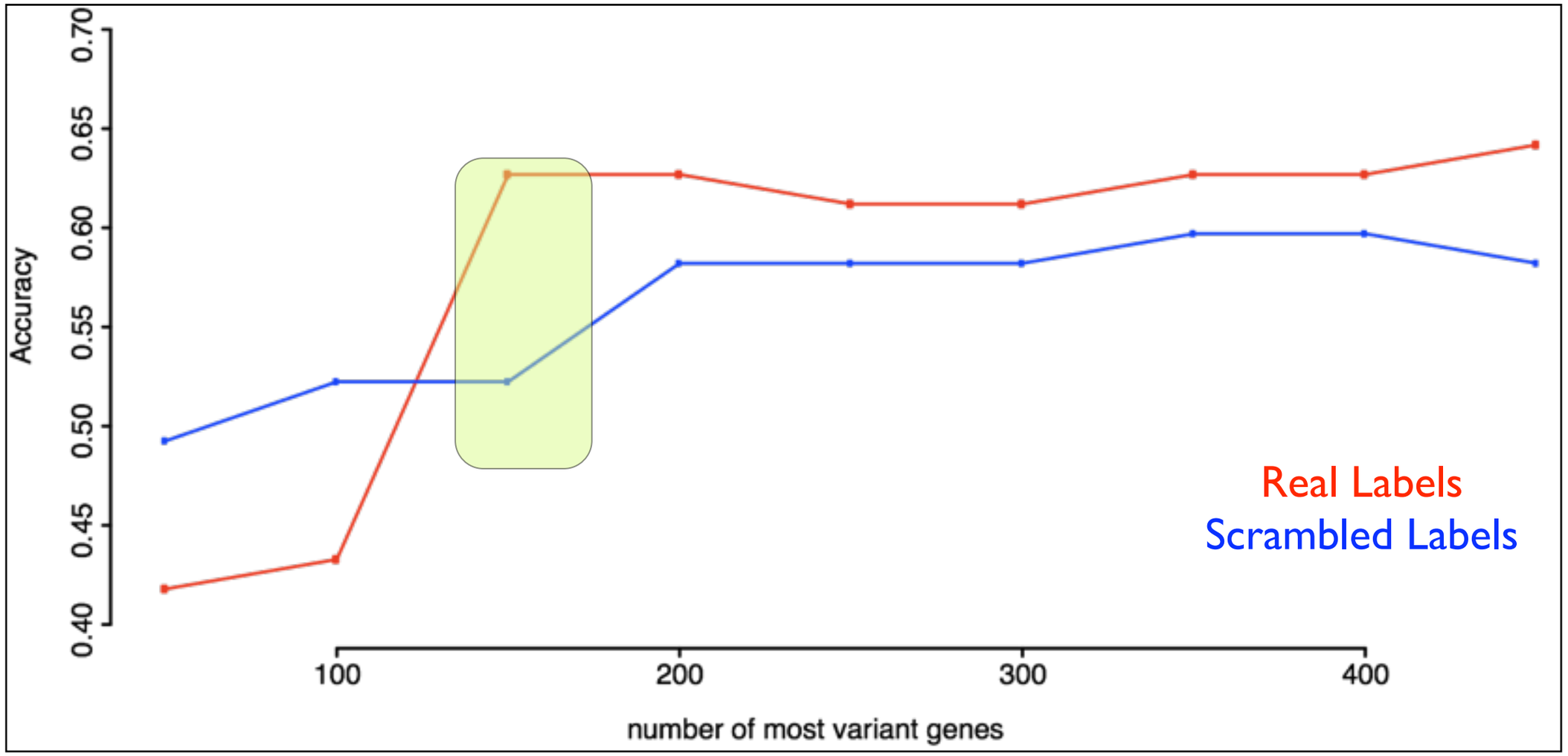


Progranulin is Highly Expressed in Peripheral Blood



Ann Neurol 2008

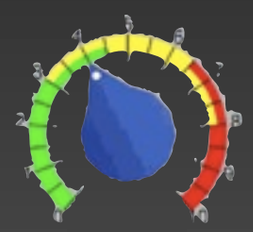
Blood-Based Molecular Classifier: Accuracy



Algorithm: Random Forests

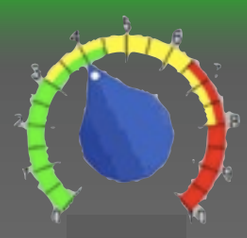
Classifier Analysis

Whole dataset

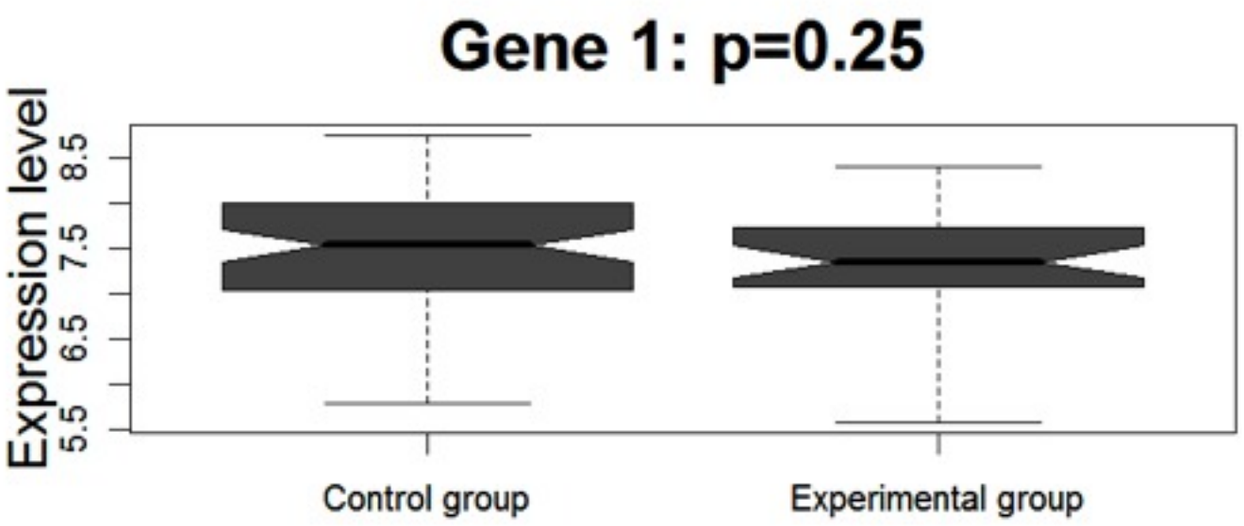


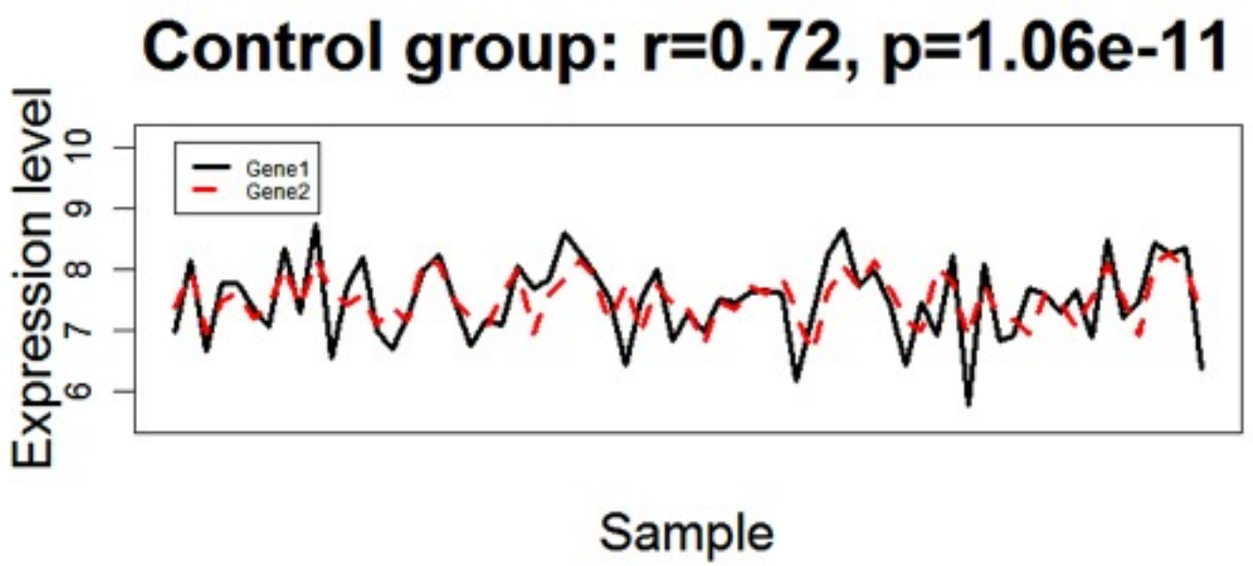
Training Set

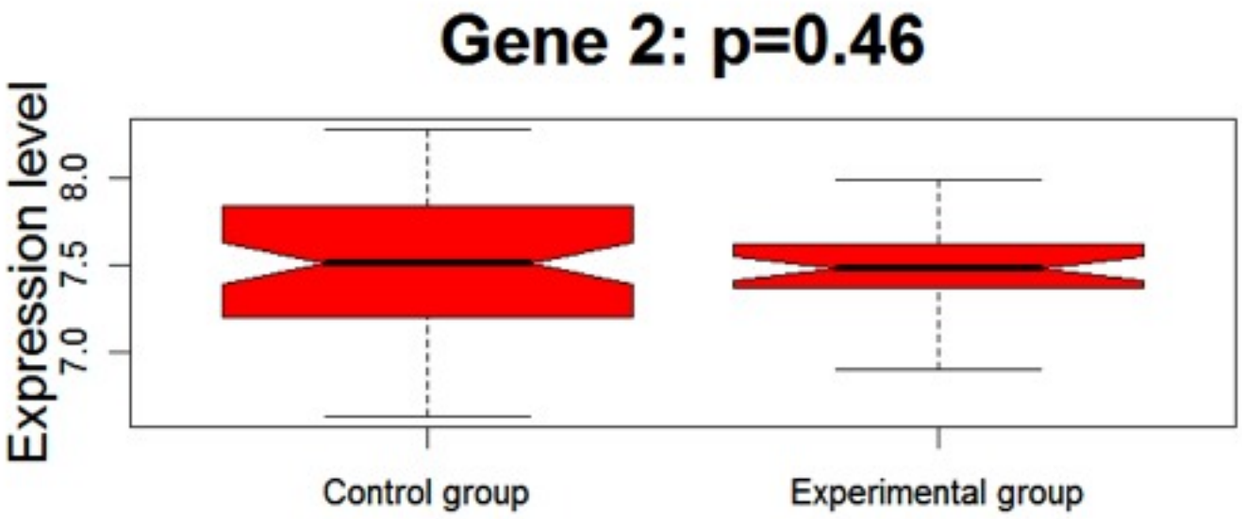
Test Set

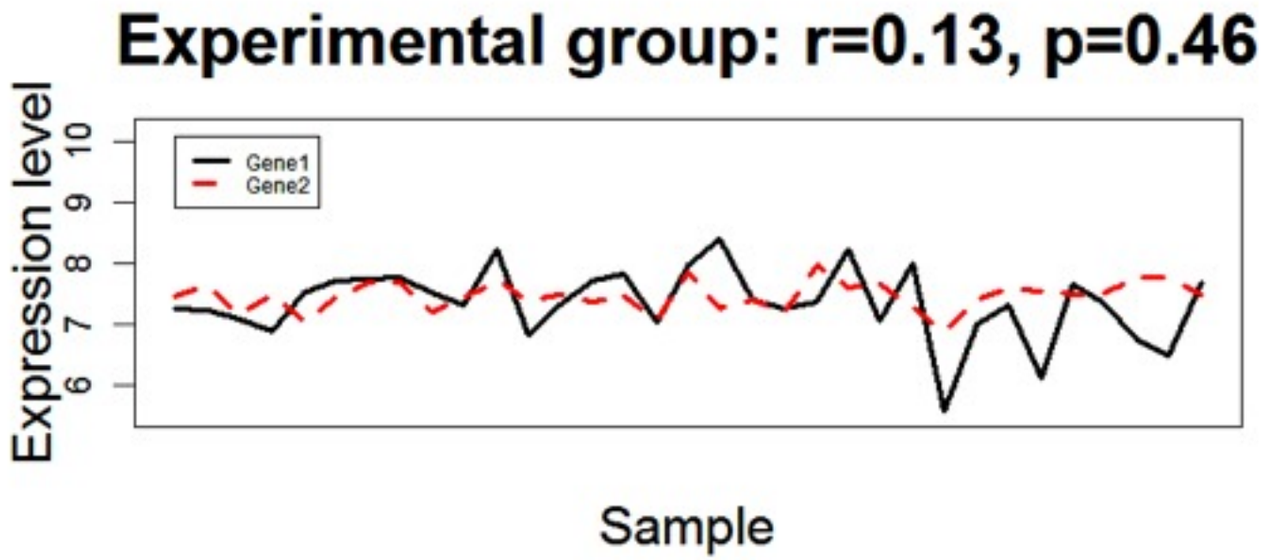


Differential Expression vs. Differential Co-Expression



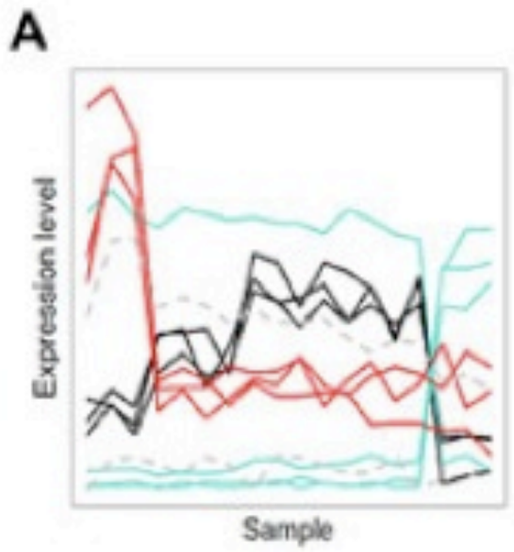


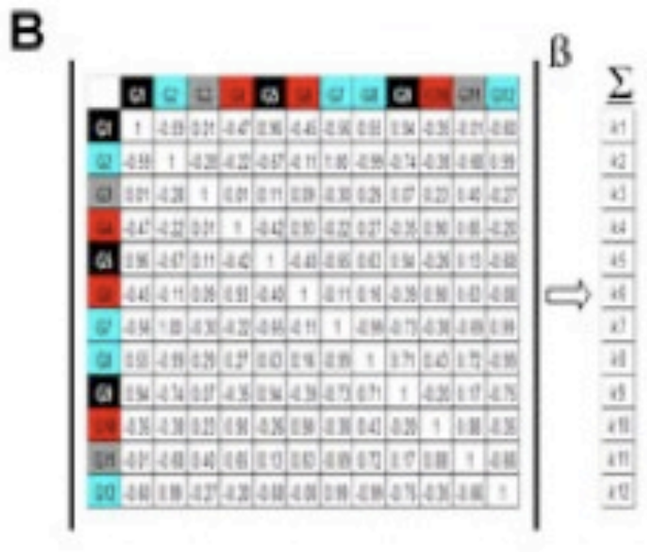


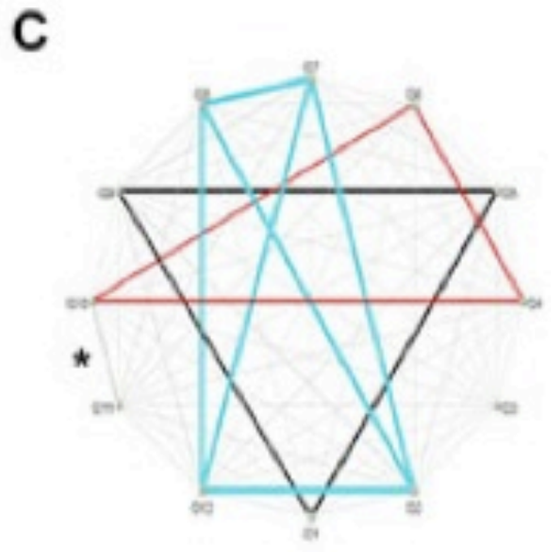


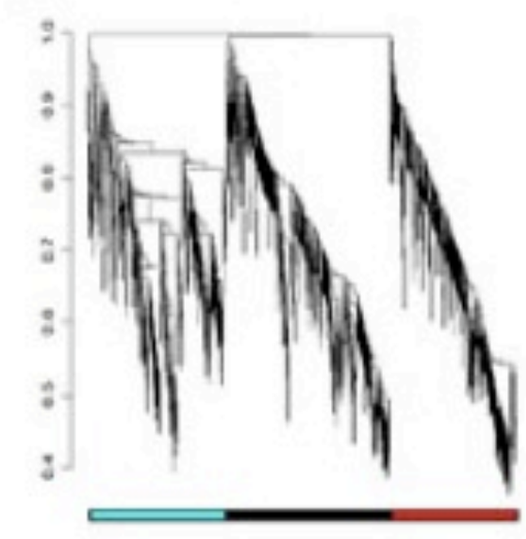
Mike Oldham
Steve Horvath

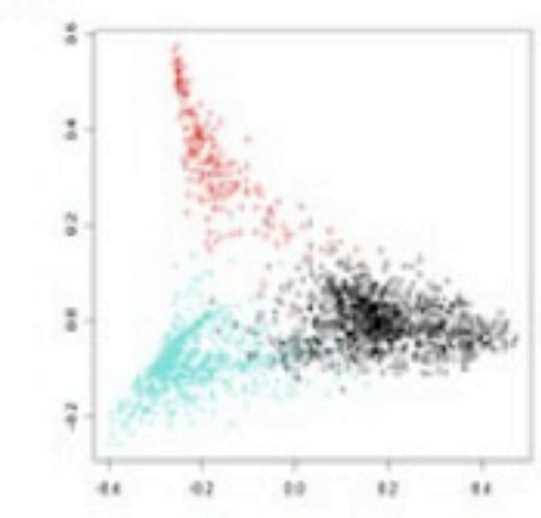
Reducing the Complexity: Gene Coexpression Networks

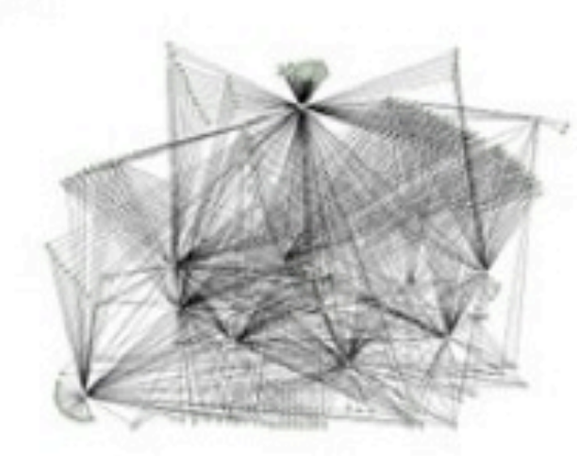






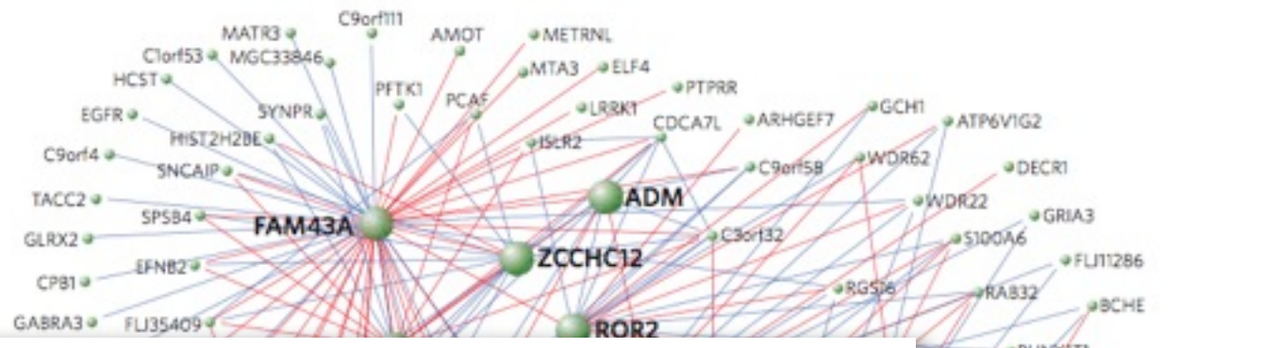


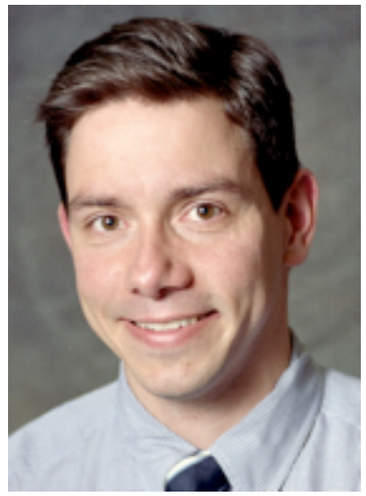




Oldham et a, *PNAS* 2006

Weighted Gene Coexpression Network Analysis (WGCNA)





Steve Horvath, PhD

Conservation and evolution of gene coexpression networks in human and chimpanzee brains

Michael C. Oldham*†‡, Steve Horvath§¶, and Daniel H. Geschwind†‡¶

ARTICLES

nature neuroscience

Functional organization of the transcriptome in human brain

Michael C Oldham[1,2], Geneviev
Steve Horvath[4–6] & Daniel H G

Molecular Systems Biology 5; Article number 291; doi:10.1038/msb.2009.46
Citation: *Molecular Systems Biology* 5:291
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www.molecularsystemsbiology.com

molecular systems biology

The organization of the transcriptional network in specific neuronal classes

Kellen D Winden[1,2,3], Michael C Oldh
Steve Horvath[4,10] and Daniel H Ges

Vol 462|12 November 2009|doi:10.1038/nature08549 nature

LETTERS

Human-specific transcriptional regulation of CNS development genes by FOXP2

Genevieve Konopka[1,3], Jamee M. Bomar[1,3], Kellen Winden[1,3], Giovanni Coppola[3], Zophonias O. Jonsson[5], Fuying Gao[3], Sophia Peng[3], Todd M. Preuss[6], James A. Wohlschlegel[5] & Daniel H. Geschwind[1,2,3,4]

OMICs Approaches to Human CNS Disease

Genetics

Genotyping
Sequencing

Epigenetics

Methylome
Histone Modifications

Gene Expression

Transcriptome
Proteome

Imaging

- Structural
- Functional

Clinical Phenotype

- Binary
- Quantitative

Neuropathology

OMICs Approaches to Human CNS Disease

Genetics

Genotyping
Sequencing

unidimensional approach

Epigenetics

Phenotypic data

Gene expression data

Epigenetic data

Copy number data

Sequence data

Imagi

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Proteome

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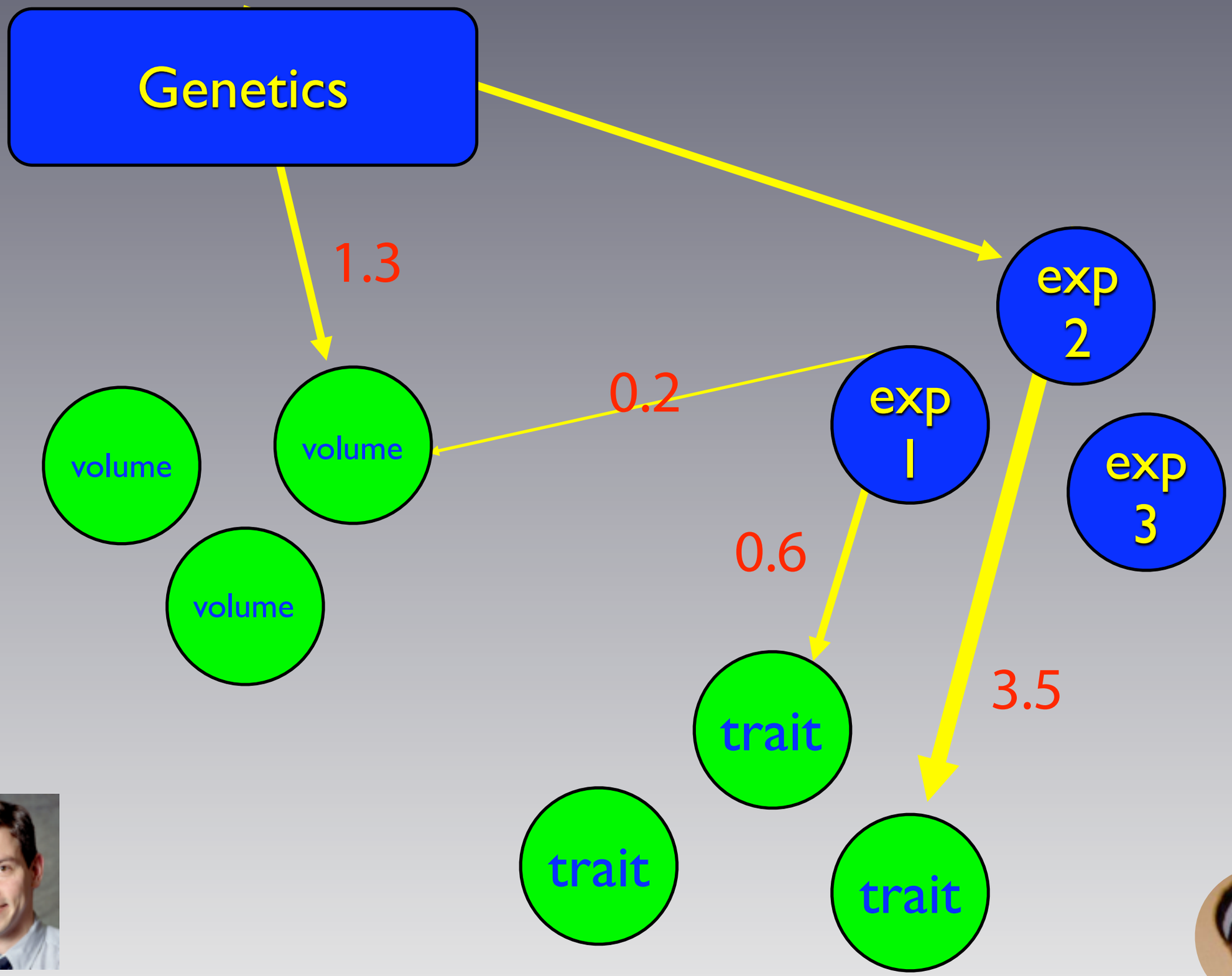
systems biology approach

ogy

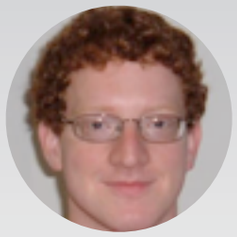
Geschwind and Konopka, Nature 2010

Network Edge Orienting (NEO)



Steve Horvath
Aten et al, BMC Systems Biol 2008

Neel Parikshak



Jason Stein

Thank You

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