

**McKnight  
Inter-Institutional  
Meeting**


**April 2015**

**Epigenomics Core –What the Core can do  
for you. Translational potential**

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Dept of Human Genetics  
Hussman Institute for Human Genomics  
University of Miami**

# Summary of last year's MBI presentation

- Our preliminary studies indicate that in mice, parental (F0) methamphetamine exposure and maternal care induce unique behavioral phenotypes in F1, F2 and F3 progeny and alter hippocampal DNA methylation (F1).
- These findings support the hypothesis that METH causes transgenerational effects through epigenetic mechanisms.

 Molecular Psychiatry (2015) 20, 252–262  
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[www.nature.com/mp](http://www.nature.com/mp)

**ORIGINAL ARTICLE**

Long-term parental methamphetamine exposure of mice influences behavior and hippocampal DNA methylation of the offspring

Y Itzhak<sup>1</sup>, I Ergui<sup>2</sup> and JI Young<sup>2,3</sup>

The high rate of methamphetamine (METH) abuse among young adults and women of childbearing age makes it imperative to

# Exaggerated claims of clinical relevance and unrealistic translational timelines

The public and funding agencies prize the rapid translation of basic biological science and animal studies into human health benefits.

It remains unclear yet whether similar epigenetic dynamics operate in rodents and humans

Important to complement animal-based epigenetic research with human studies



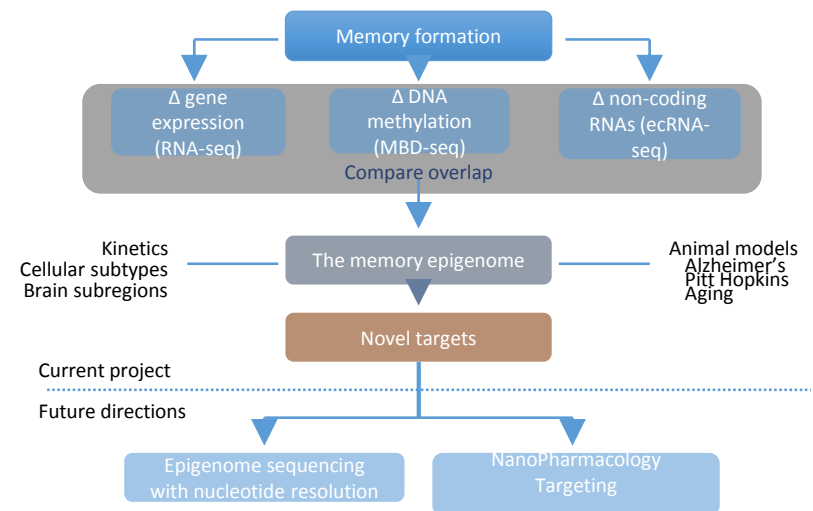
The image shows a screenshot of a BBC News article. At the top, the BBC logo is visible on the left, and 'Sign in' is on the right. Below the logo is a red banner with the word 'NEWS' in white. Underneath the banner is a navigation bar with links for 'Home', 'Video', 'World', 'US & Canada', 'UK', and 'Business'. The article is categorized under 'Health'. The headline is "'Memories' pass between generations" by James Gallagher, a health and science reporter for BBC News. The article features a photograph of three women and a baby, representing different generations. Below the photo, the text states: "Behaviour can be affected by events in previous generations which have been passed on through a form of genetic memory, animal studies suggest." It further explains that experiments showed a traumatic event could affect the DNA in sperm and alter the brains and behaviour of subsequent generations. A partial sentence at the bottom reads: "A Nature Neuroscience study shows mice trained to avoid a smell passed their..."

# Translational potential

A comparative encyclopedia of DNA elements in the mouse genome

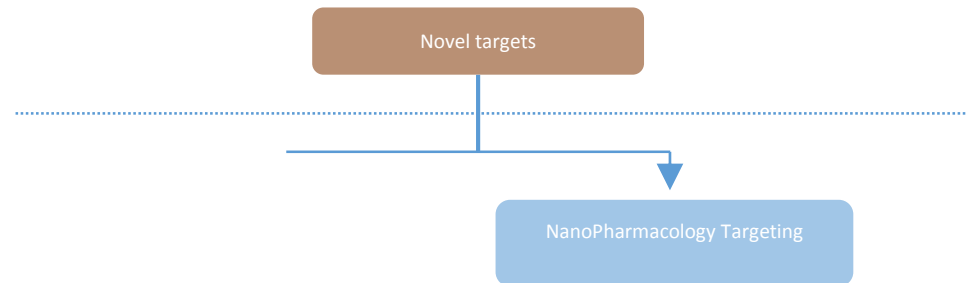


- Chromatin state landscape in a cell lineage is relatively stable in both human and mouse.
- Chromatin domains, are developmentally stable and evolutionarily conserved.



# Translational potential

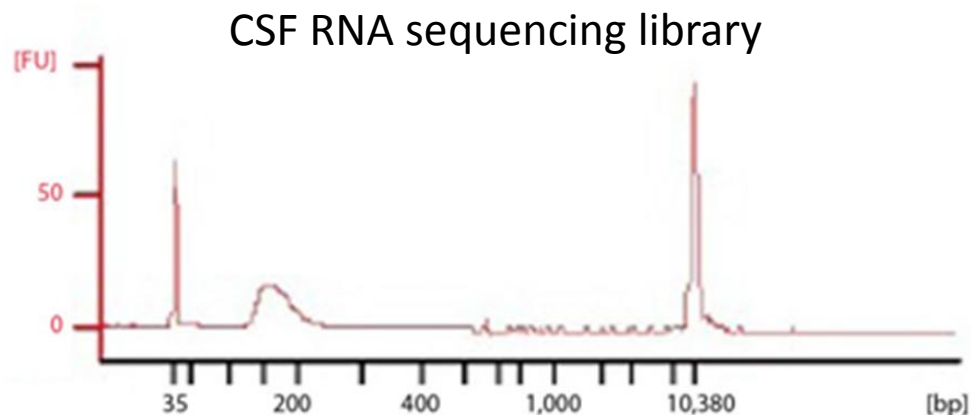
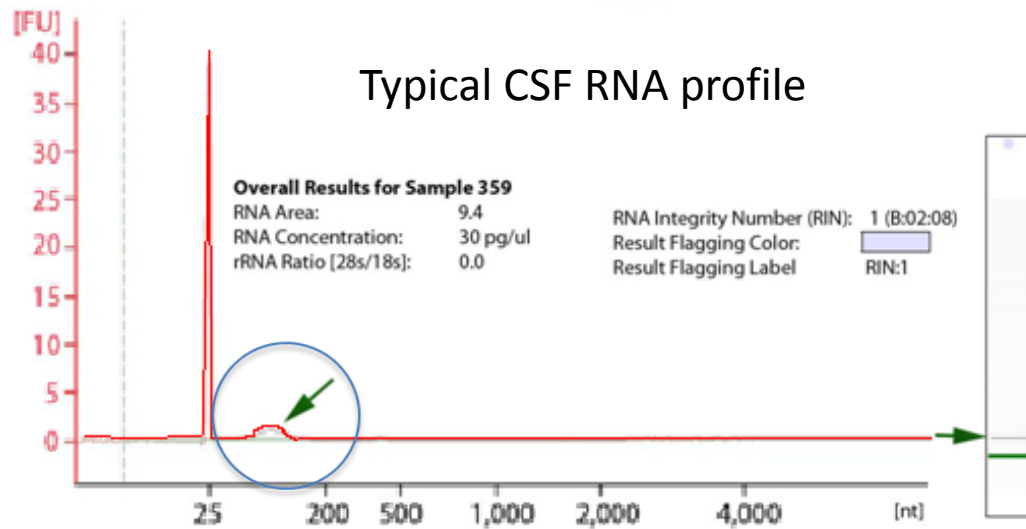
- Validated molecular biomarkers of human aging
  - novel targets
  - could be used to test effects of interventions



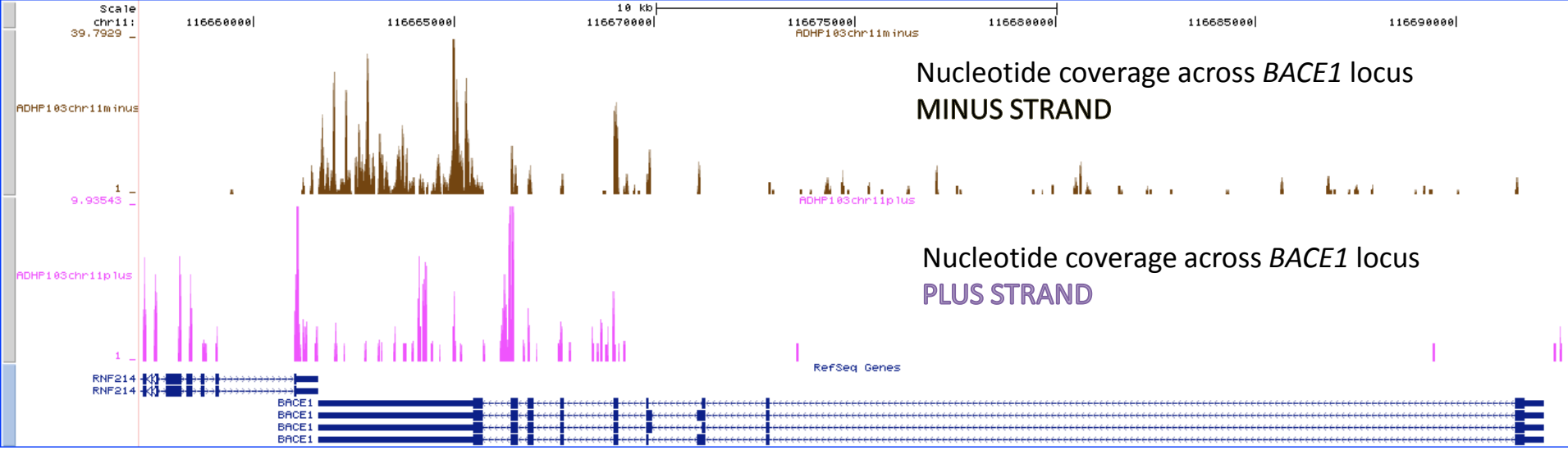
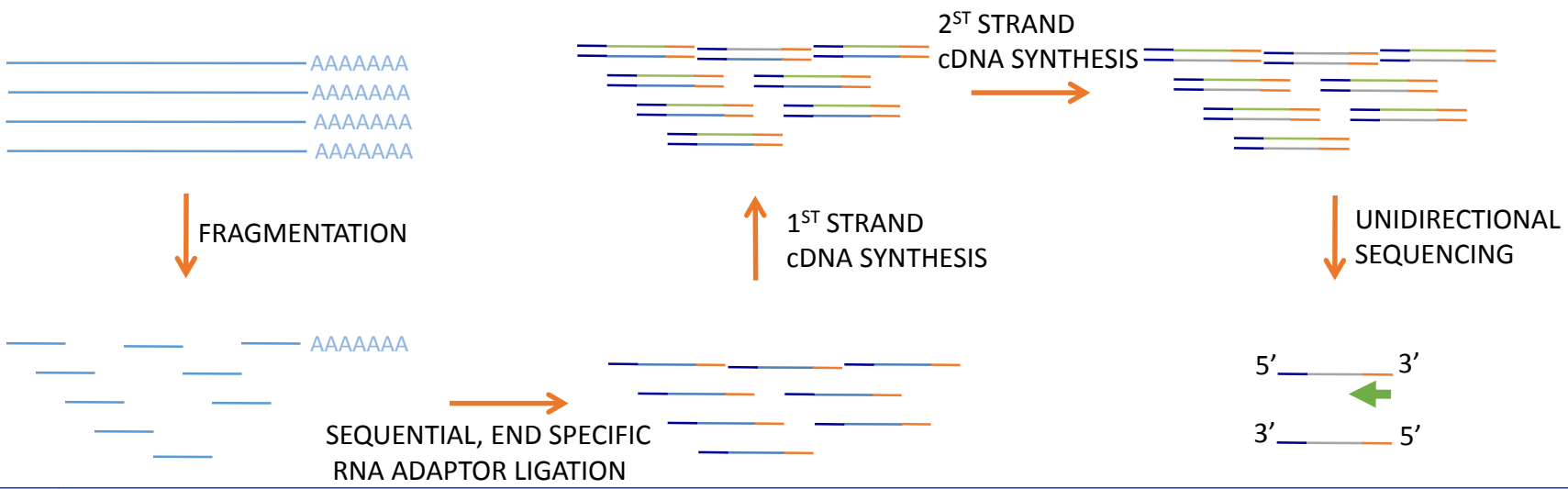
- Circulating RNA
- DNA methylation.

# Biomarker potential of RNA transcripts in CSF

Peripheral biofluids such as cerebrospinal fluid and serum might contain markers of central nervous system disorders.



# Modified library prep yields directional mRNAseq data



- Similar levels of coverage to standard RNAseq
- Able to resolve Sense-antisense pairings
- More accurate quantitation – counts attributed to one transcript only

# Biomarker potential of RNA transcripts in CSF

- We processed 57 CSF samples received from VA Puget Sound Health Care system. (68-89 y.o.)
- We performed extracellular RNA extraction and directional RNA-seq library preparation.
- we utilized an optimized NEB-based directional mRNA-Seq sample preparation kit to prepare all libraries.
- The directional approach generated in average 67 million pair-end reads using the Illumina HiSeq 2000 platform
- Bioinformatics Analysis of the data

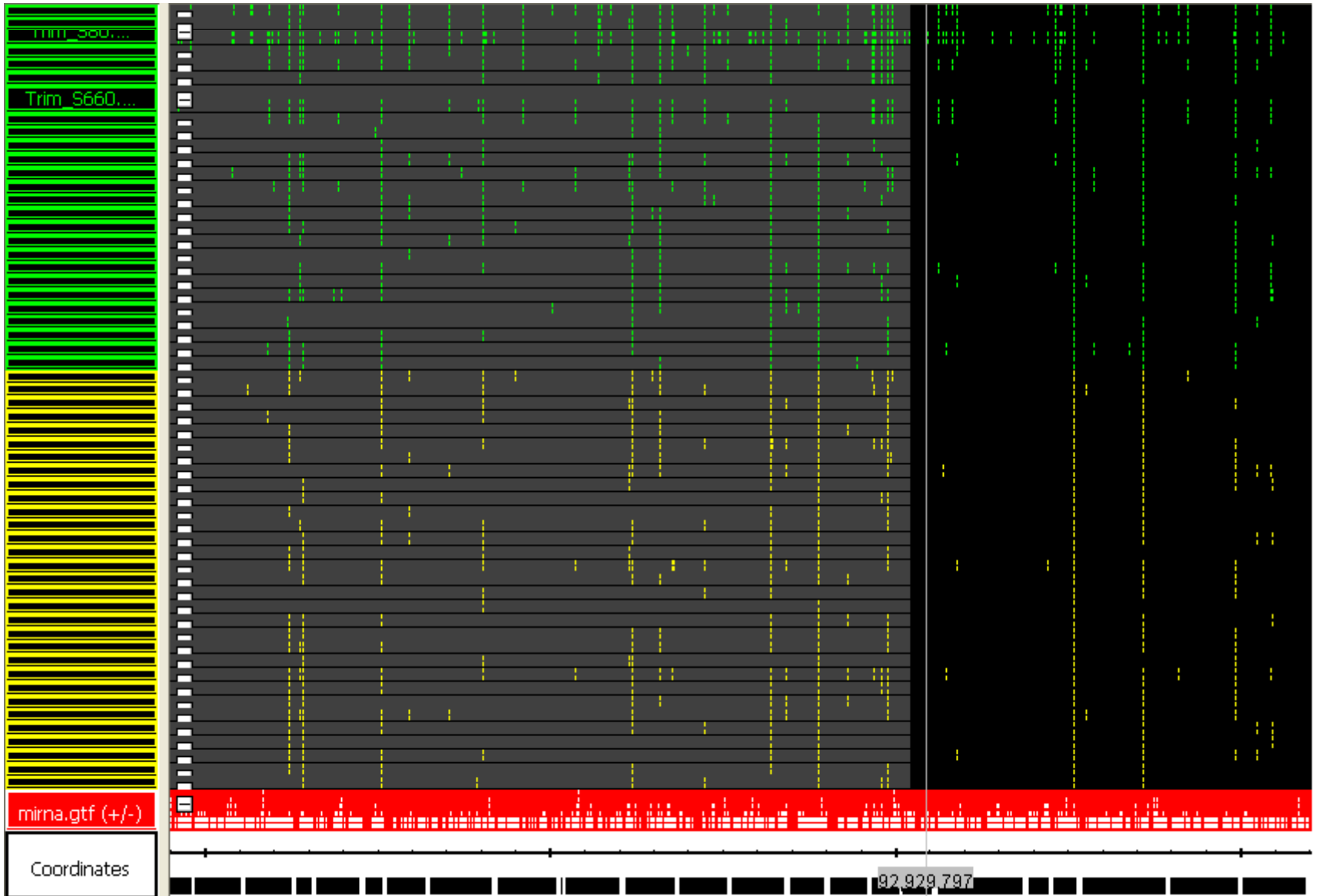
## Transcriptome of the human CSF

- We sought to ascertain the defining transcriptome of the human CSF by identifying a set of transcript present in all CSF samples analyzed (irrespective of disease status) at similar levels.
- We have found 454 gene transcripts present in all samples with no significant difference between sample groups.
- Interestingly, the most enriched GO molecular function is voltage-gated channel activity as identified by EnrichR (<http://amp.pharm.mssm.edu/Enrichr/enrich>).

# of genes	Known %	Novel %	Protein coding %	ncRNA %
454	89.2	10.8	80.4	19.6

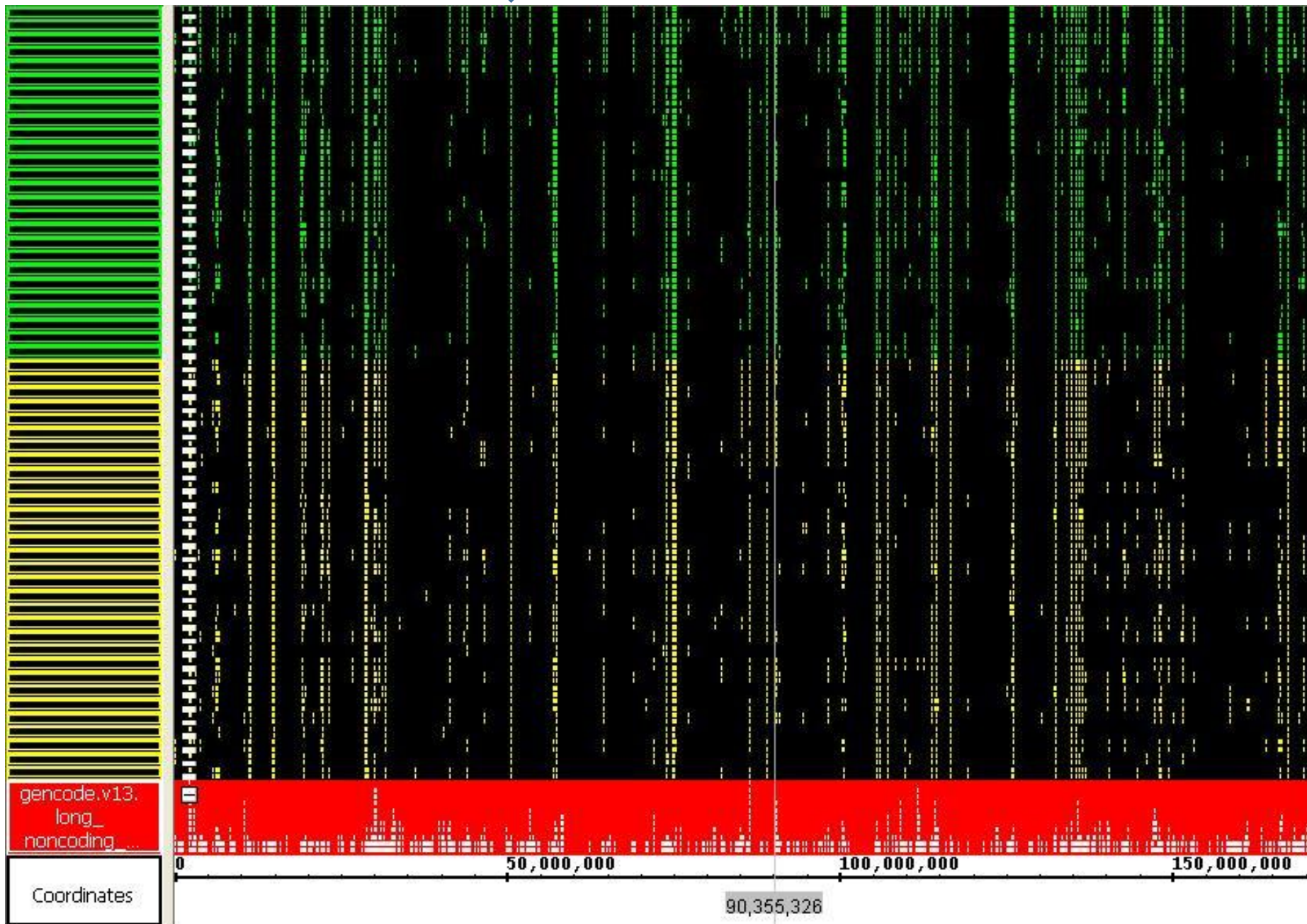
# miRNA full genome

↓ MIR3201



# lncRNAs – chromosome 6

↓ RP11-524K22.1



# Biomarker potential of RNA transcripts in CSF



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**Description** No description available (442 genes)

## Human Gene Atlas

[Bar Graph](#) **[Table](#)** [Grid](#) [Network](#)

Hover each row to see the overlapping genes.

10 entries per page

Search:

Index	Name	P-value	Z-score	Combined Score
1	CerebellumPeduncles	0.005550	-1.58	8.20
2	Cerebellum	0.01918	-1.22	4.81
3	UterusCorpus	0.04226	-1.17	3.70

## GO Molecular Function

[Bar Graph](#) **[Table](#)** [Grid](#) [Network](#)

Hover each row to see the overlapping genes.

10 entries per page

Search:

Index	Name	P-value	Z-score	Combined Score
1	voltage-gated channel activity (GO:0022832)	0.00002676	-2.45	13.09
2	voltage-gated ion channel activity (GO:0005244)	0.00002676	-2.44	13.03
3	voltage-gated cation channel activity (GO:0022843)	0.00001044	-2.35	12.56
4	cation channel activity (GO:0005261)	0.00005112	-2.45	12.23
5	substrate-specific channel activity (GO:0022838)	0.0001412	-2.49	10.44
6	passive transmembrane transporter activity (GO:0022803)	0.0002668	-2.48	10.38
7	channel activity (GO:0015267)	0.0002668	-2.47	10.33
8	gated channel activity (GO:0022836)	0.0002156	-2.45	10.23
9	metal ion transmembrane transporter activity (GO:0046873)	0.0003216	-2.43	10.09
10	ion channel activity (GO:0005216)	0.0002852	-2.41	10.08

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**Description** No description available (442 genes)

## KEGG 2015

[Bar Graph](#) **[Table](#)**

Hover each row to see the overlapping genes.

10 entries per page

Search:

Index	Name	P-value	Z-score	Combined Score
1	calcium signaling pathway	0.001232	-2.01	4.82
2	ecm receptor interaction	0.006234	-1.81	2.65
3	cell communication	0.01440	-1.80	1.87
4	aminoacyl trna biosynthesis*	0.03702	-1.66	1.17
5	bladder cancer*	0.04178	-1.64	1.16
6	long term depression*	0.04947	-1.51	1.07
7	type ii diabetes mellitus*	0.04684	-1.50	1.06

**DAVID Bioinformatics Resources 6.7**  
National Institute of Allergy and Infectious Diseases (NIAID), NIH

## Functional Annotation Chart

[Help and Manual](#)

Current Gene List: List\_1  
Current Background: Homo sapiens  
377 DAVID IDs

Options

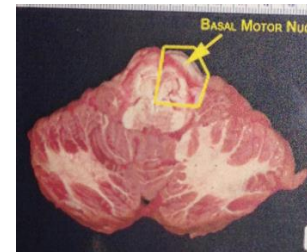
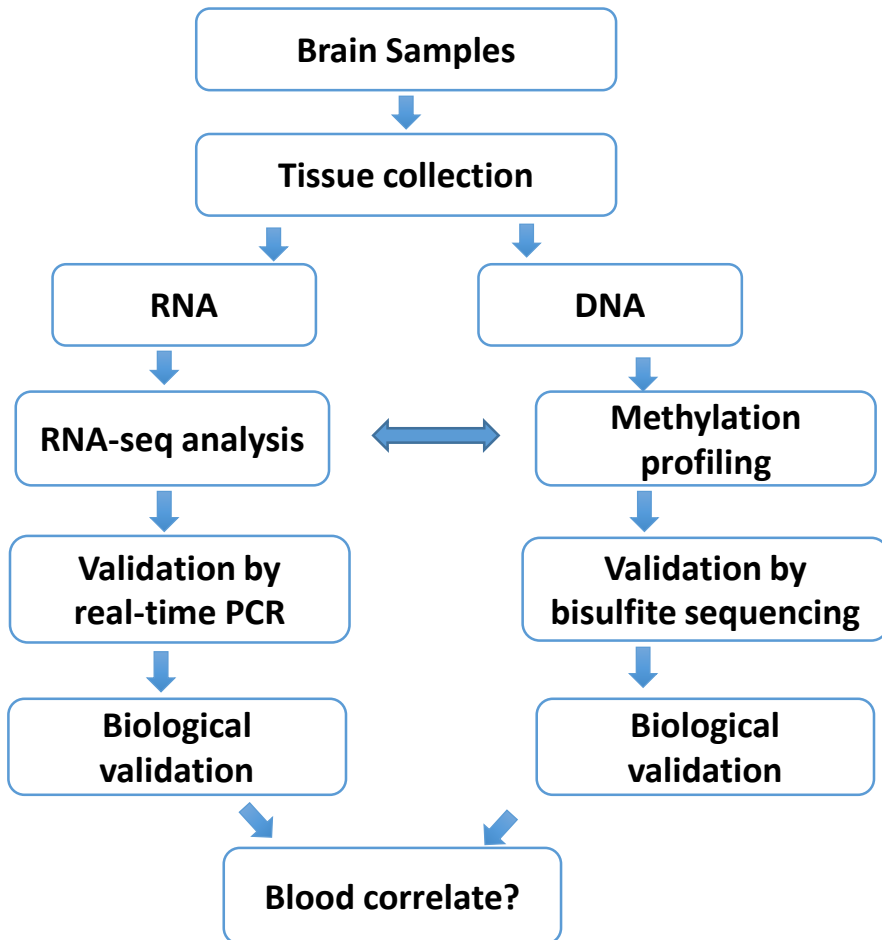
[Rerun Using Options](#) [Create Sublist](#)

33 chart records

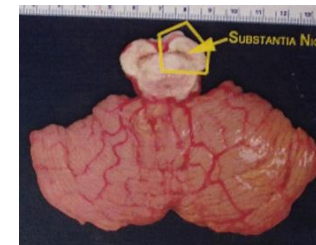
Sublist	Category	Term	RT	Genes	Count	%	P-Value	Benjamin
<input type="checkbox"/>	GOTERM_CC_FAT	<a href="#">cation channel complex</a>	RT	13	3.4	1.5E-5	4.6E-3	
<input type="checkbox"/>	GOTERM_CC_FAT	<a href="#">calcium channel complex</a>	RT	6	1.6	1.8E-4	2.8E-2	
<input type="checkbox"/>	GOTERM_CC_FAT	<a href="#">voltage-gated calcium channel complex</a>	RT	5	1.3	9.0E-4	8.8E-2	
<input type="checkbox"/>	GOTERM_CC_FAT	<a href="#">ion channel complex</a>	RT	13	3.4	9.7E-4	7.1E-2	

# Genome wide profiling of CpG methylation in brain samples.

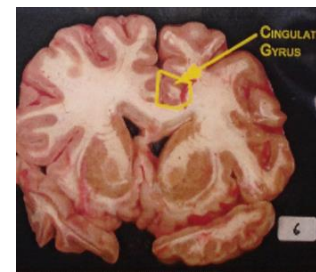
- Dorsal motor nucleus of the vagus



- Substantia nigra

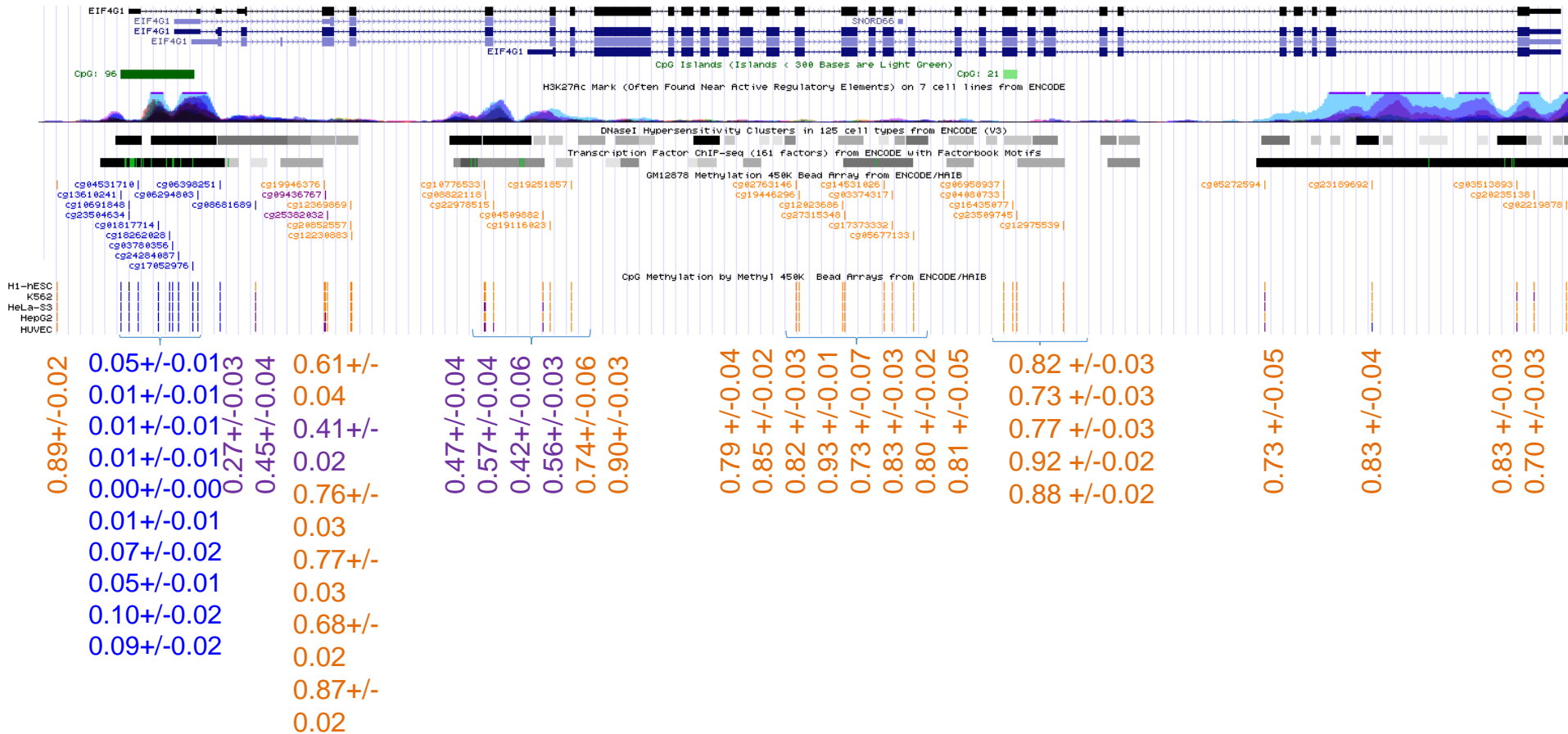


- Cingulate cortex



63-86 y.o.

# EIF4G1



Methylation was recorded as a fraction between zero and one, representing the frequency of methylation of a given CpG marker.

# Changes in the methylome associate with age of the donor

- 1.05% of the markers had significant associations between methylation value and age ( [FDR] < 0.05).

## KEGG 2015

Bar Graph **Table** ⚙

Hover each row to see the overlapping genes.

10 entries per page

Search:

Index	Name	P-value	Z-score	Combined Score
1	gap junction	0.009331	-1.97	0.59
2	small cell lung cancer	0.02371	-1.87	0.56
3	melanoma	0.03820	-1.84	0.56
4	non small cell lung cancer*	0.05065	-1.73	0.52

## GO Cellular Component

Bar Graph **Table** Grid Network ⚙

Hover each row to see the overlapping genes.

10 entries per page

Search:

Index	Name	P-value	Z-score	Combined Score
1	chromosome (GO:0005694)	0.003507	-2.34	1.02
2	receptor complex (GO:0043235)	0.01471	-2.31	1.00
3	dendrite (GO:0030425)	0.01340	-2.30	1.00
4	side of membrane (GO:0098552)	0.005163	-2.29	0.99
5	adherens junction (GO:0005912)	0.02737	-2.21	0.96
6	blood microparticle (GO:0072562)	0.05880	-2.14	0.93
7	external side of plasma membrane (GO:0009897)	0.02271	-2.14	0.93
8	extracellular region (GO:0005576)	0.07061	-2.11	0.92

## OMIM Disease

Bar Graph **Table** Grid Network ⚙

Hover each row to see the overlapping genes.

10 entries per page

Search:

Index	Name	P-value	Z-score	Combined Score
1	adenoma*	0.04337	-1.70	0.70
2	parkinson_disease*	0.08979	-1.35	0.56
3	schizophrenia*	0.1454	-1.19	0.49
4	blood*	0.1908	-1.12	0.46
5	ataxia*	0.3801	2.91	-1.20
6	ectodermal_dysplasia*	0.2268	3.01	-1.25
7	epilepsy*	0.3646	3.03	-1.25

## Summary

- Through CSF-RNA transcriptome profiling and brain tissue methylation profiling we have identified potential biomarkers with reproducible recovery and reliable measurements

# Acknowledgements

- [The Morris K. Udall Parkinson Disease Research Center of Excellence](#)
- Jeff Vance
- Claes Wahlestedt
- Mohammad Faghigi
- Arash Hossein