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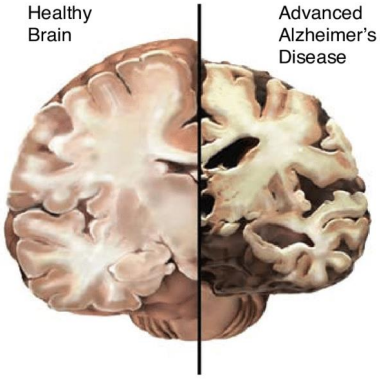
Differentially expressed transcript regions in Alzheimer‘s disease

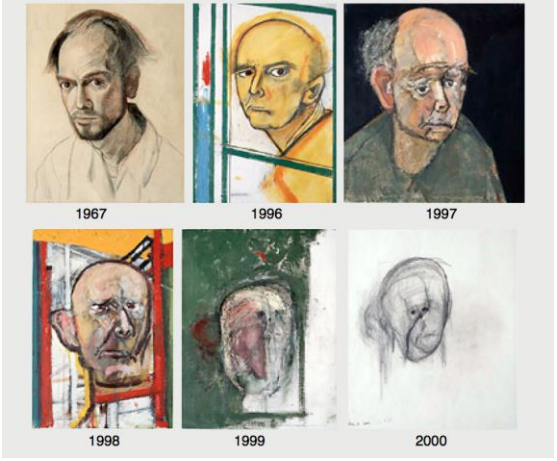
Bled, 14 February 2020

Leipzig University, Bioinformatik
Natasha Jorge

ALZHEIMER‘S DISEASE (AD)

- Chronic neurodegenerative disease
- Memory loss, language problems, disorientation, mood swings
- Cause is unknown – plaques and neurofibrilary tangles
- No cure





New Results

Alzheimer related genes show accelerated evolution

Anne Nitsche, Kristin Reiche, Uwe Ueberham, Christian Arnold, Jörg Hackermüller, Friedemann Horn, Peter F. Stadler, Thomas Arendt

doi: https://doi.org/10.1101/114108

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with control samples [Supplementary Methods]. Applying this custom array to 19 AD patients and 22 control samples, we identified a differential expression of 154 multi-exonic cRNAs with a total of 4,162 splice sites and 141 multi-exonic lncRNAs with a total of 1,297 splice sites.

New Results

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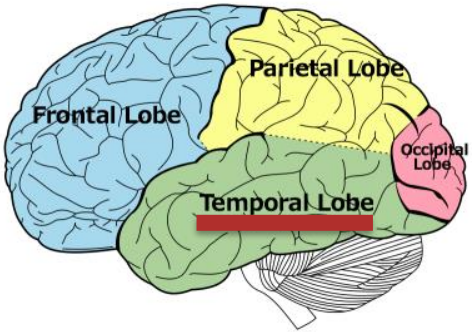
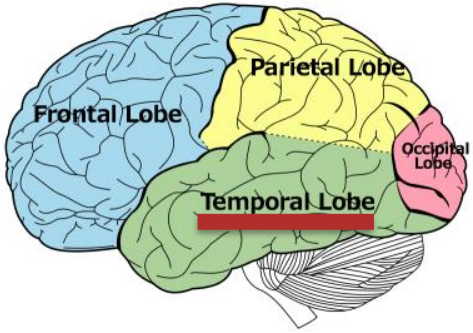
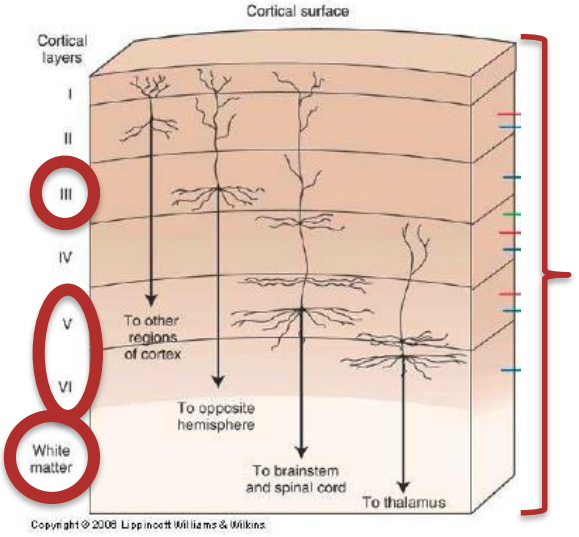
OBJECTIVES

IDENTIFY ALTERNATIVE USAGE OF 3’ ENDS

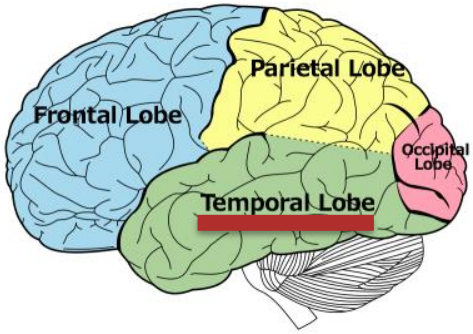
MATERIAL AND METHODS

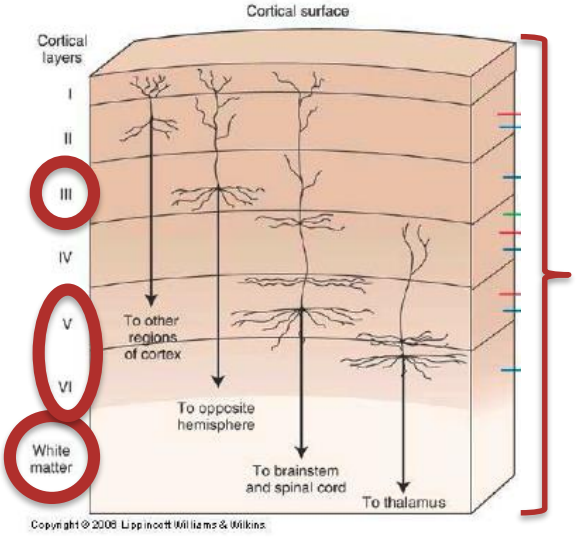



Parietal Lobe
Frontal Lobe
Occipital Lobe
Temporal Lobe


Cortical surface
Cortical layers
I
II
III
IV
V
VI
White matter
To other regions of cortex
To opposite hemisphere
To brainstem and spinal cord
To thalamus
Copyright © 2008 Lippincott Williams & Wilkins

Whole Brain



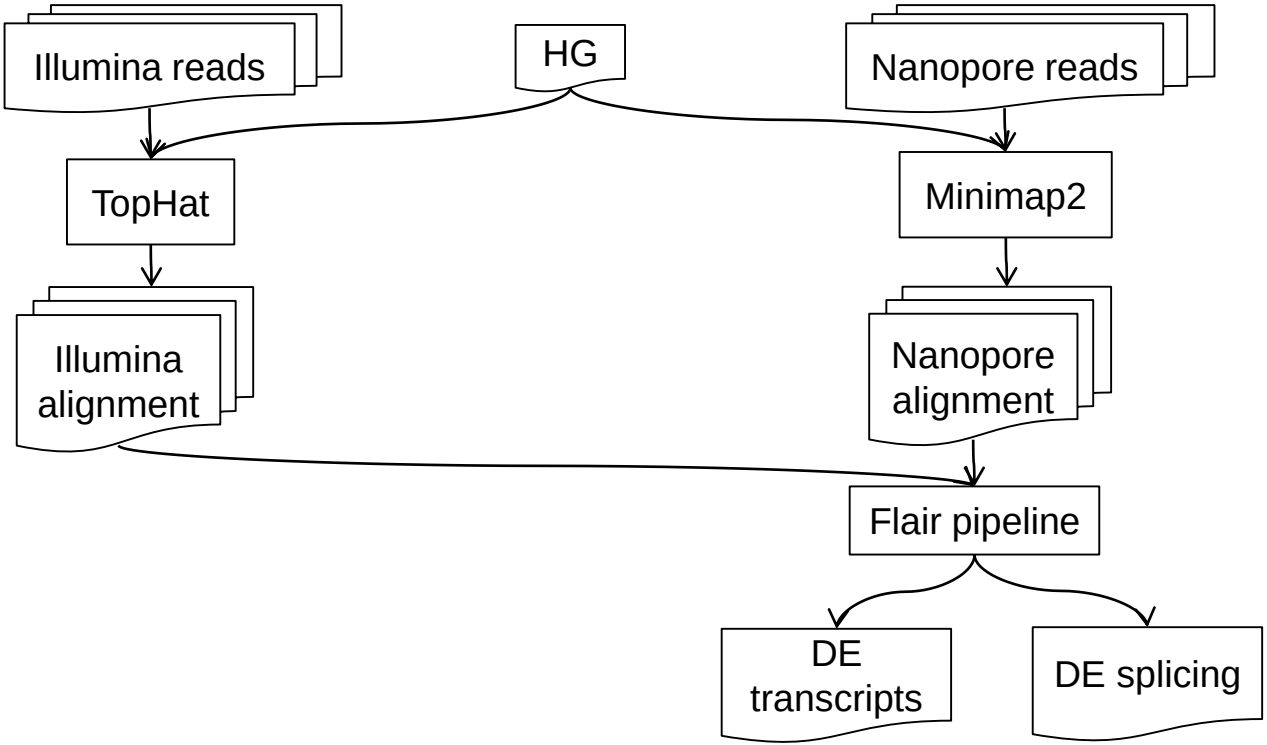


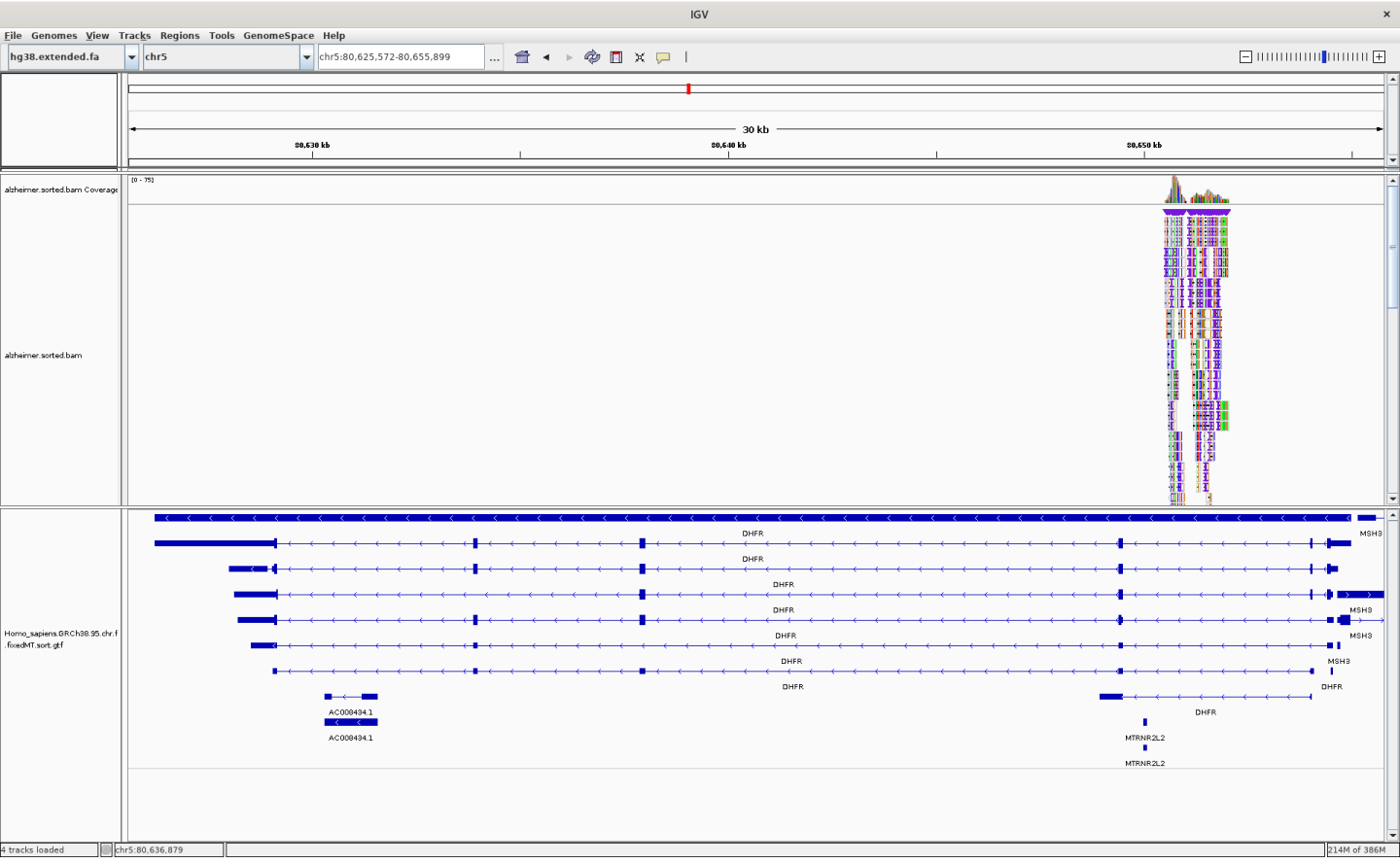
Whole Brain

illumina®

Oxford NANOPORE Technologies

DRS


Illumina reads
HG
Nanopore reads
TopHat
Minimap2
Illumina alignment
Nanopore alignment
Flair pipeline
DE transcripts
DE splicing


IGV
File Genomes View Tracks Regions Tools GenomeSpace Help
hg38.extended.fa
chr5
chr5:80,625,572-80,655,899
30 kb
80,630 kb
80,640 kb
80,650 kb
alzheimer.sorted.bam Coverage
alzheimer.sorted.bam
Homo_sapiens.GRCh38.95.chr.f
.fixedMT.sort.gtf
DHFR
MSH3
AC008434.1
MTRNR2L2
4 tracks loaded
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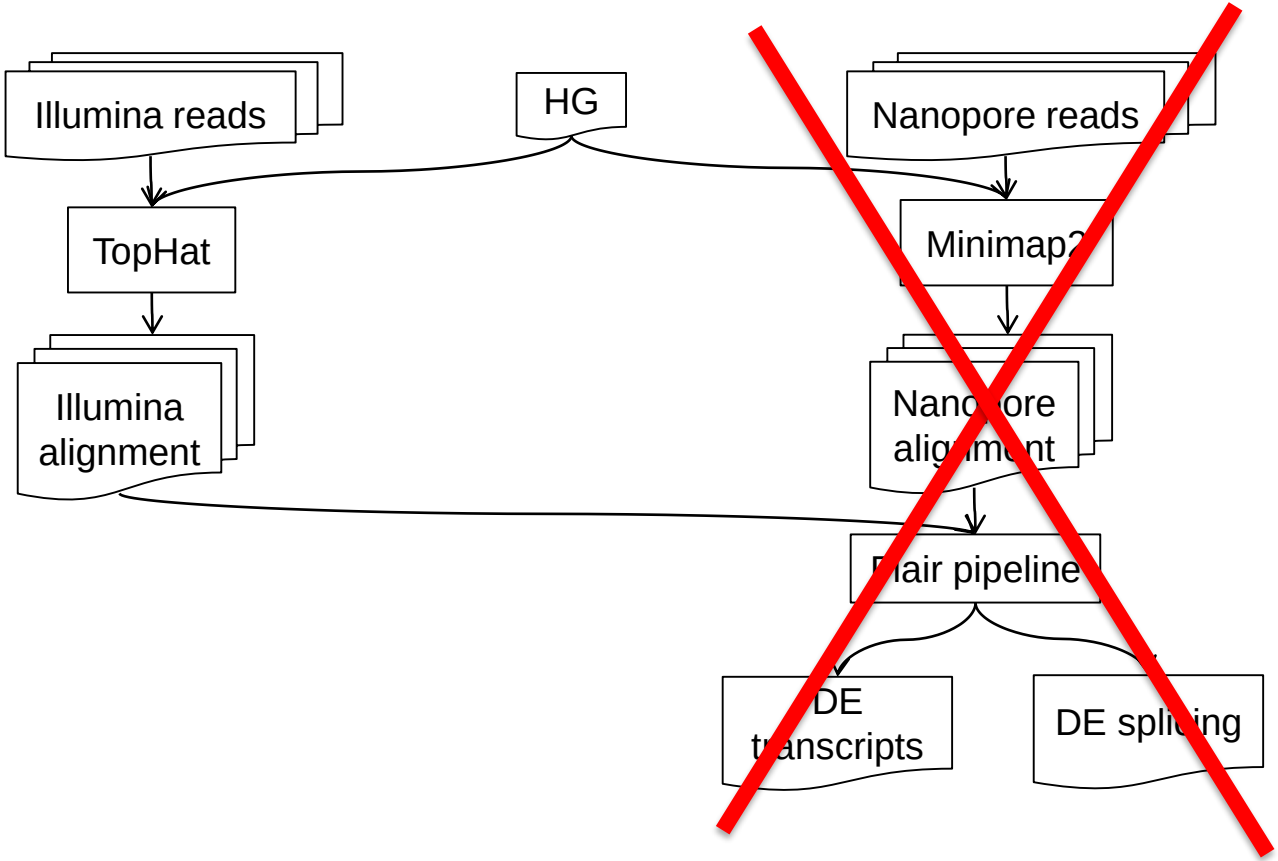
214M of 386M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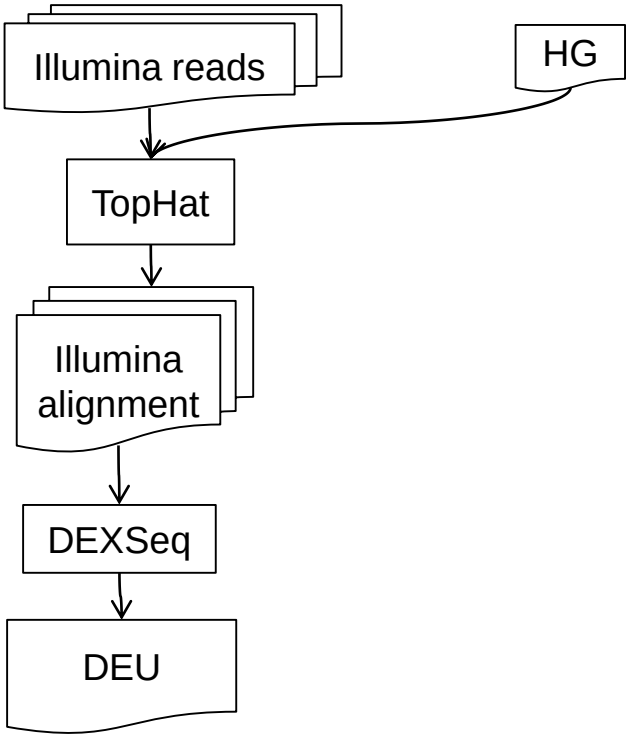
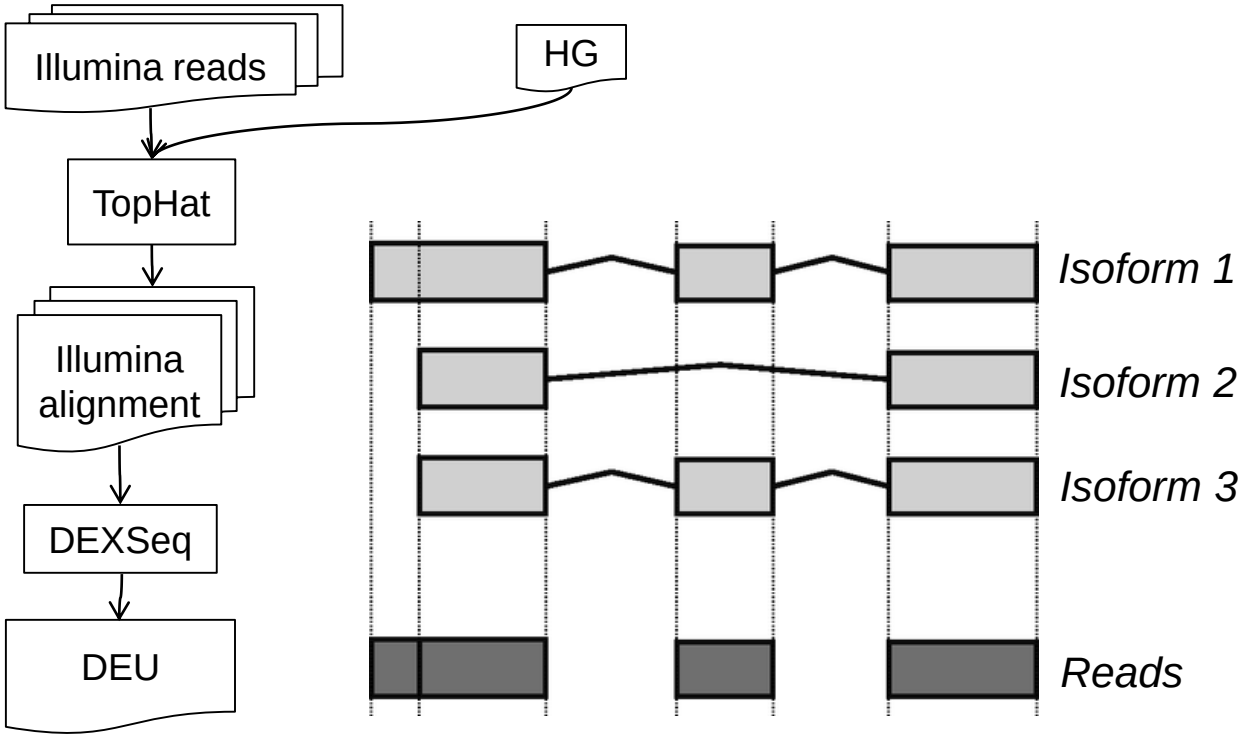
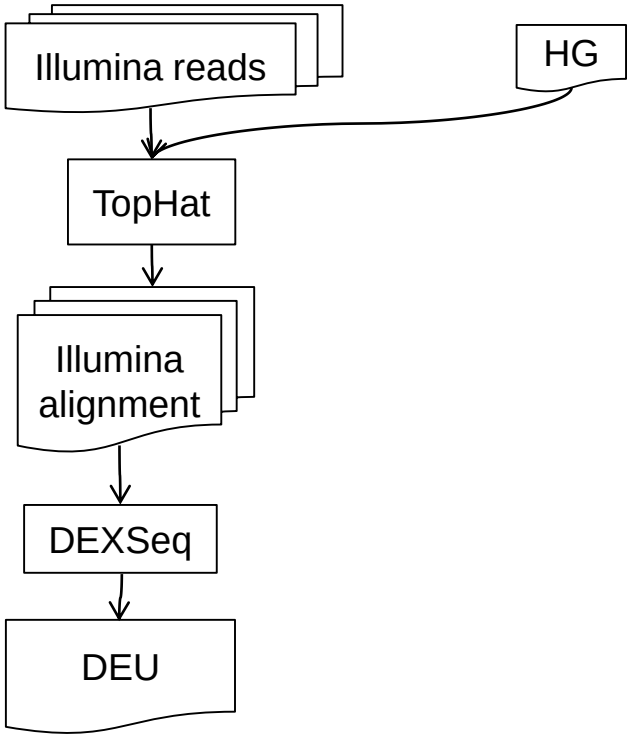
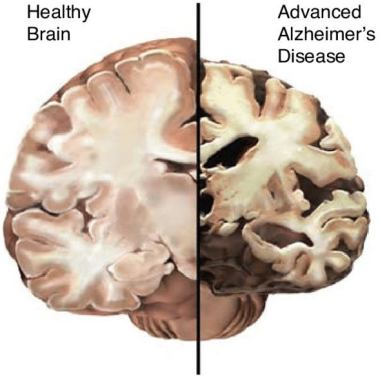
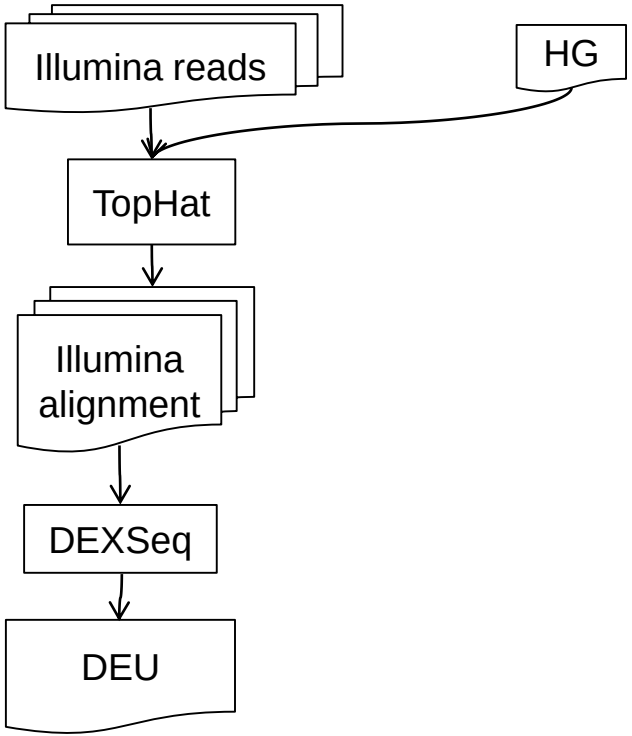
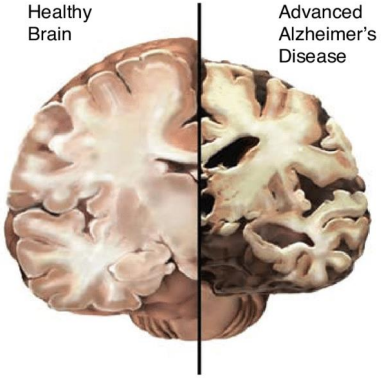

Illumina reads
HG
TopHat
Illumina alignment
DEXSeq
DEU


Illumina reads
HG
TopHat
Illumina alignment
DEXSeq
DEU
Isoform 1
Isoform 2
Isoform 3
Reads


Illumina reads
HG
TopHat
Illumina alignment
DEXSeq
DEU


Healthy Brain
Advanced Alzheimer's Disease


Illumina reads
HG
TopHat
Illumina alignment
DEXSeq
DEU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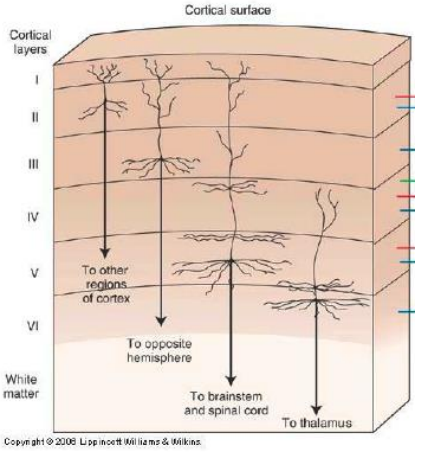
Cortical surface
Cortical layers
I
II
III
IV
V
VI
White matter
To other regions of cortex
To opposite hemisphere
To brainstem and spinal cord
To thalamus
Copyright © 2008 Lippincott Williams & Wilkins

RESULTS PER CONDITION

Region	Number of DE regions
Layer III	52
Area V and VI	34
White Matter	61
Whole Brain	3

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Layer III	52
Area V and VI	34
White Matter	***61***
Whole Brain	3

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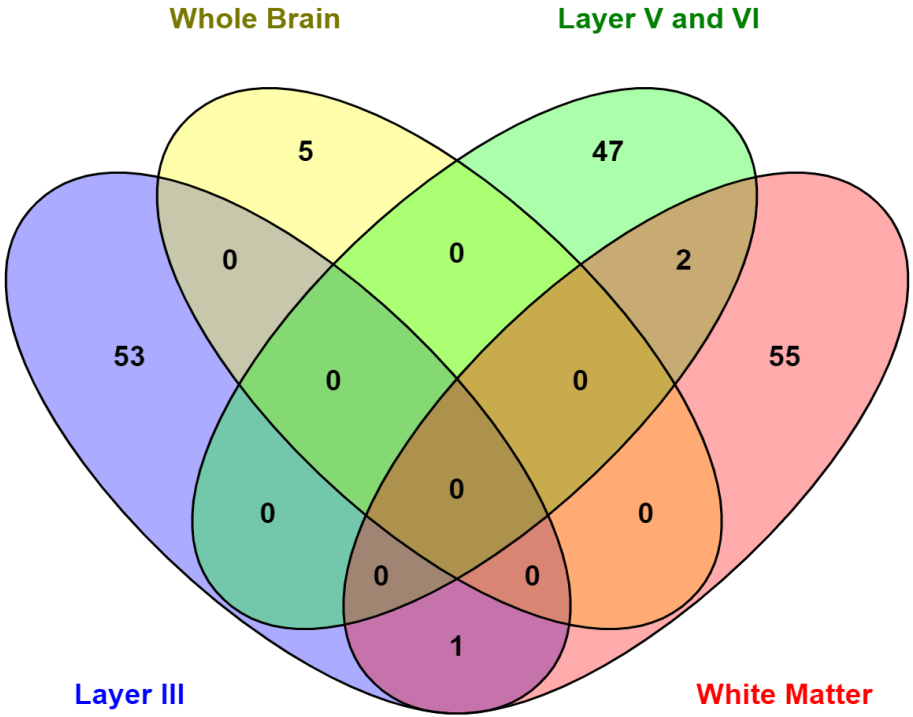
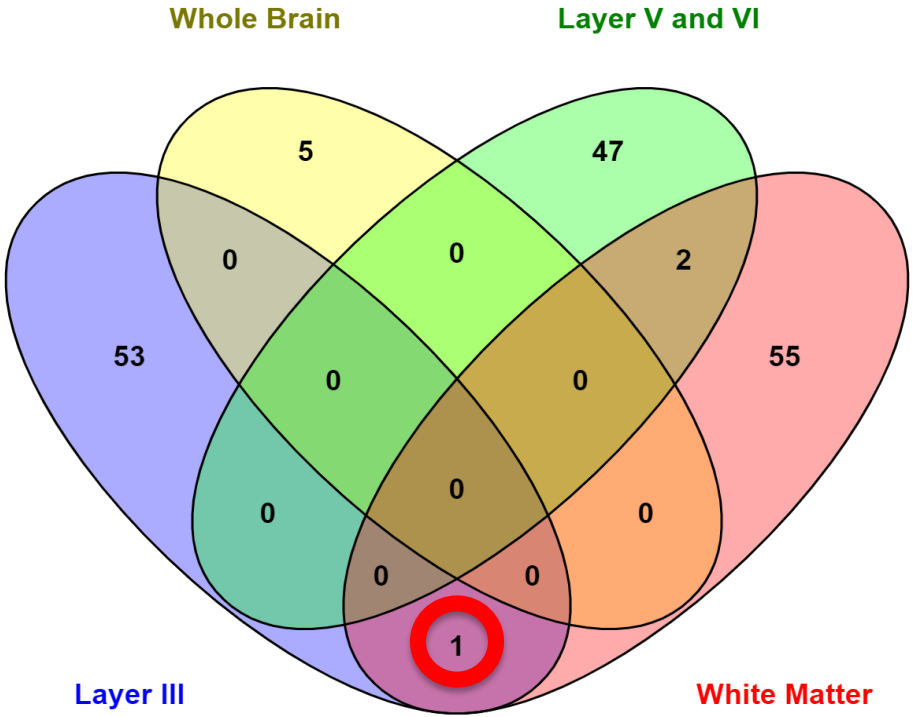
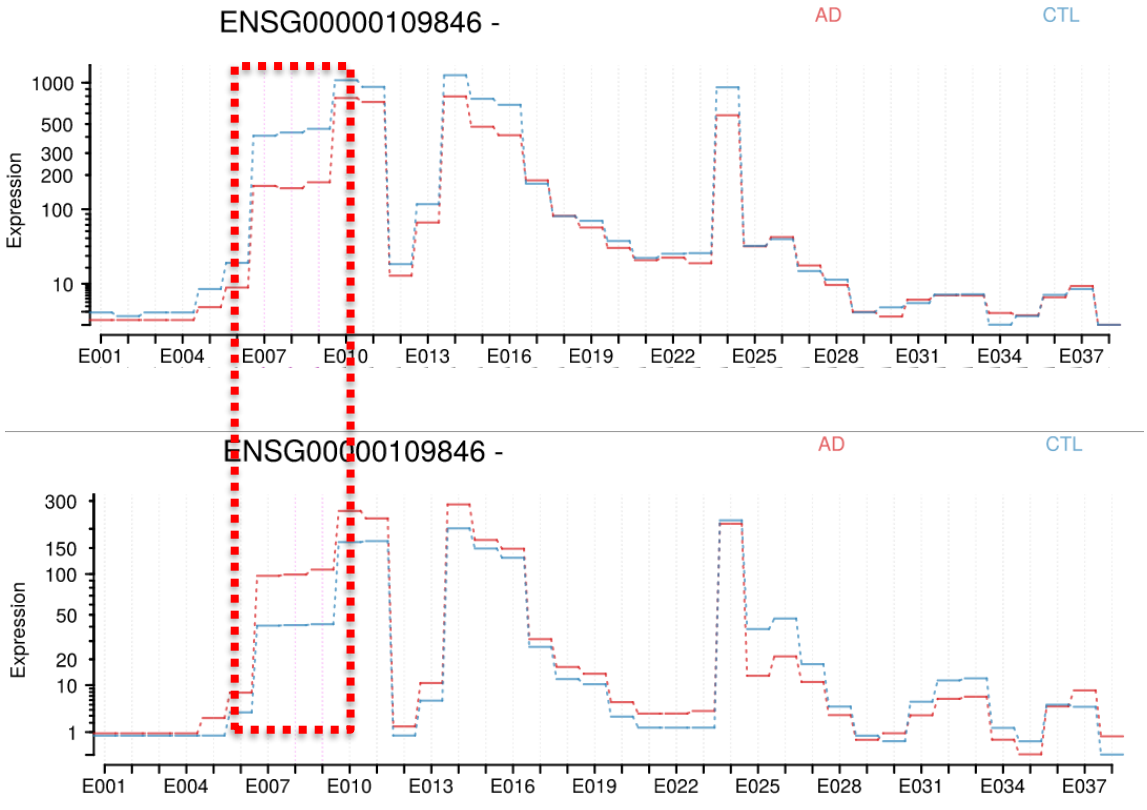
White Matter	61
Whole Brain	***3***


Whole Brain
Layer V and VI
5
47
0
0
2
53
0
0
55
0
0
0
0
0
1
Layer III
White Matter


Whole Brain
Layer V and VI
5
47
0
0
2
53
55
0
0
0
0
0
0
0
1
Layer III
White Matter

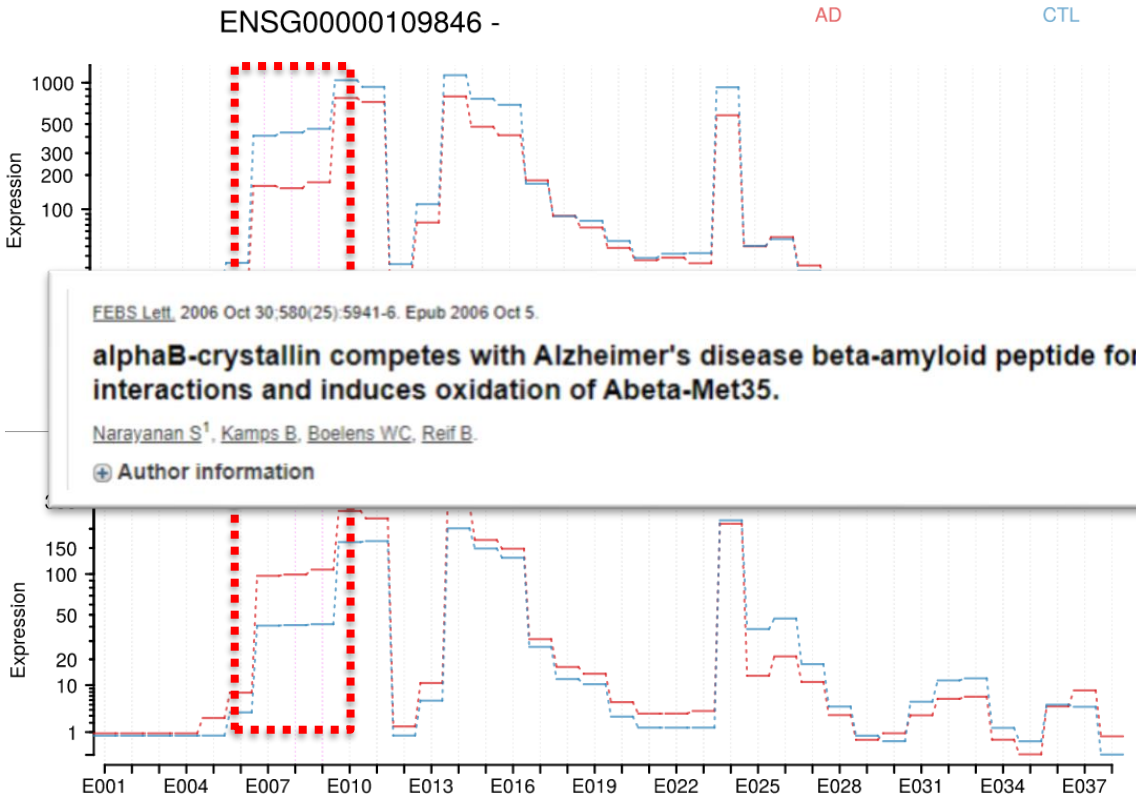
CRYAB



White Matter

Layer III

CRYAB



FEBS Lett. 2006 Oct 30;580(25):5941-6. Epub 2006 Oct 5.

alphaB-crystallin competes with Alzheimer's disease beta-amyloid peptide for peptide-peptide interactions and induces oxidation of Abeta-Met35.

Narayanan S[1], Kamps B, Boelens WC, Reif B.

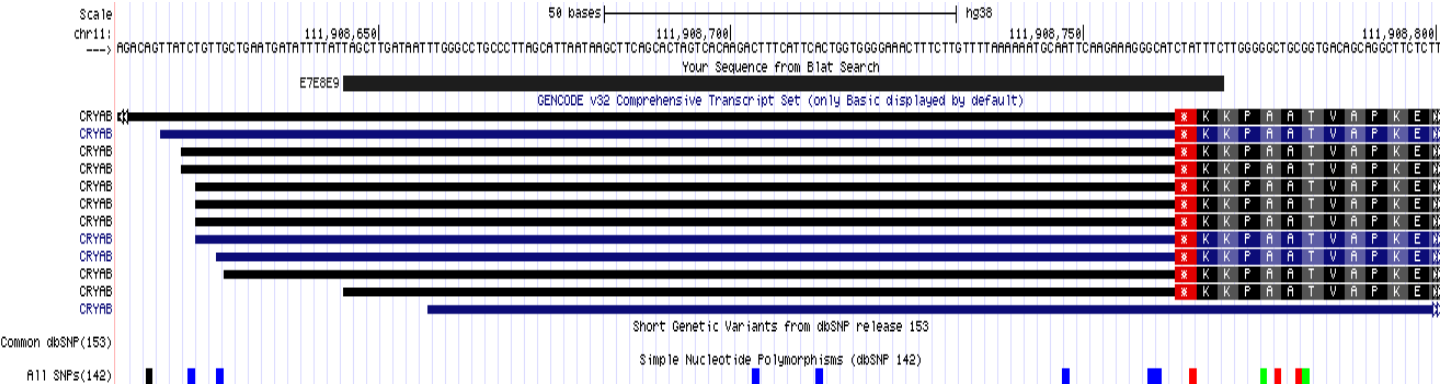
⊕ Author information

Layer III

CRYAB

Scale
50 bases
hg38
chr11:
111,908,650
111,908,700
111,908,750
111,908,800
Your Sequence from Blat Search
E7E8E9
GENCODE v32 Comprehensive Transcript Set (only Basic displayed by default)
CRYAB
Short Genetic Variants from dbSNP release 153
Common dbSNP(153)
Simple Nucleotide Polymorphisms (dbSNP 142)
All SNPs(142)

CRYAB



63 miRNAs - TargetScan

Region	Number of DE regions	Genomic context
Layer III	52	23 introns 2 5’ UTR 20 3’ UTR
Area V and VI	34	14 introns 5 5’ UTR 8 3’ UTR
White Matter	61	22 introns 2 5’ UTR 15 3’ UTR
Whole Brain	3	All coding exons

PRELIMINARY CONCLUSIONS

- Different brain layers show different splicing patterns;
- The small number of DEU in Whole Brain samples might be due to the natural difference amongst layers;
- The DEU in the 5’ and 3’ regions might affect the stability and gene expression control mechanisms;

FUTURE STEPS

- Fresh Brains!!!! – DRS
- Differential expressed isoforms -> Ryuto
- Identification of AD related genes
- Putative miRNA target sites
- Putative polyA sites

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VIELEN DANK!

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www.bioinf.uni-leipzig.de

RESULTS PER LAYER - AD

Comparison		Number of DE regions	Genomic Context
Whole Brain	x Layer III	23	8 introns 1 5' UTR 11 3 ' UTR
	x Layer V and VI	31	14 introns 4 5' UTR 12 3' UTR
	x White Matter	11	8 introns 0 5' UTR 6 3' UTR
Layer III	x Layer V and VI	19	9 introns 5 5' UTR 4 3' UTR
	x White Matter	18	11 intron 1 5' UTR 8 3' UTR
Layer V and VI	x White Matter	4	4 introns 0 5' UTR 1 3' UTR

RESULTS PER LAYER - CTL

Comparison		Number of DE regions	Genomic Context
Whole Brain	x Layer III	2	0 introns 0 5' UTR 1 3 ' UTR
	x Layer V and VI	60	25 introns 5 5' UTR 17 3' UTR
	x White Matter	5	4 introns 0 5' UTR 0 3' UTR
Layer III	x Layer V and VI	25	11 introns 3 5' UTR 4 3' UTR
	x White Matter	71	26 intron 5 5' UTR 19 3' UTR
Layer V and VI	x White Matter	9	5 introns 1 5' UTR 1 3' UTR