Finding epigenetic blood biomarkers for Alzheimer's Disease

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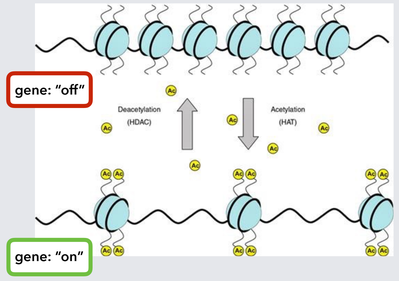
Background

Alzheimer's Disease (AD) = **immune basis in blood + brain**[1]

How can we find epigenetic AD blood biomarkers?

H3K27ac: histone acetylation, marker of nearby open chromatin[2]

- related to areas on genome that are linked to AD

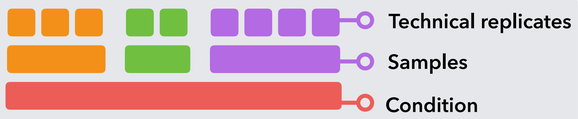


This figure[3] (adapted) shows the process of histone acetylation.

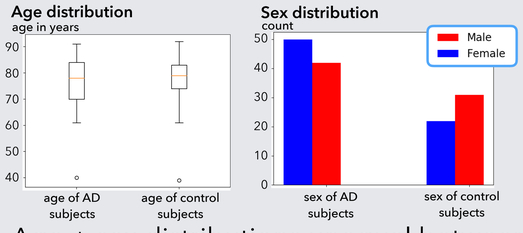
Hypothesis

Differential H3K27ac ChIP-seq peaks between AD and control samples in blood data can be used as an **epigenetic blood biomarker for AD.**

Dataset

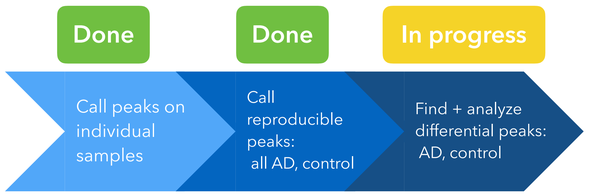


- **Buffy-coat H3K27ac ChIP-seq data - Kellis Lab @ MIT**
  - Postmortem human brain
  - Project previously designed by Pfenning Lab
- 145 subjects - 92 AD, 53 control



- Age + sex distributions unequal between AD and control

Method



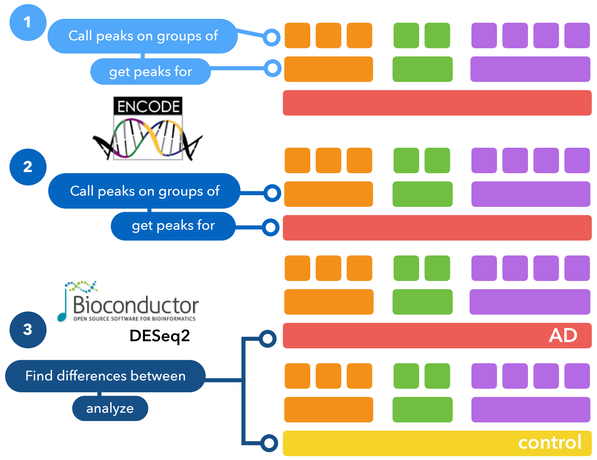
Peak calling - ENCODE ChIP-seq analysis pipeline[4]

- Automated input creation and pipeline runs

Differential peaks - DESeq2[5]

Analysis - GREAT[6], MEME-ChIP[7]

Model



Individual peak calling: results

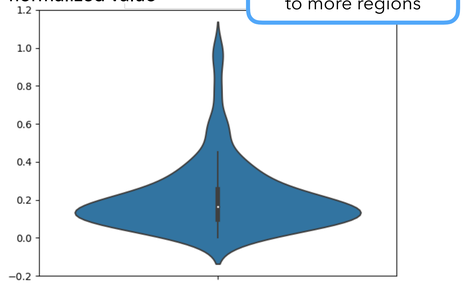
For a given *sample*, where does the histone acetylation occur?

ENCODE Pipeline process:

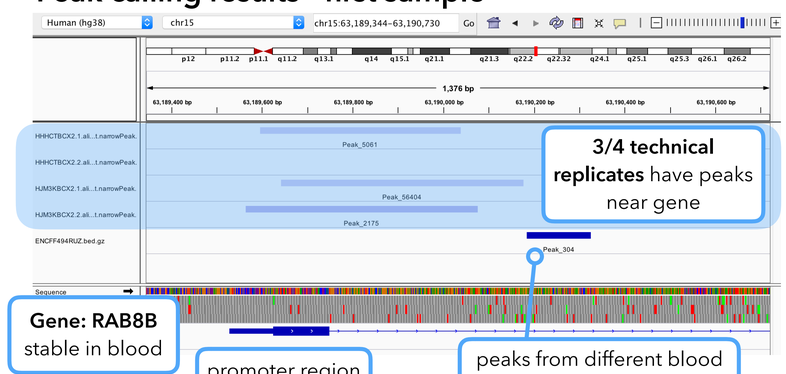
1. FASTQ (sequencing data) files aligned to genome w/ BWA[8]
2. Peaks called w/ MACS2[9]
3. QC metrics generated
   - Ex. FRiP, Reproducibility test

QC example - FRiP

(Fraction of Reads in Peaks)

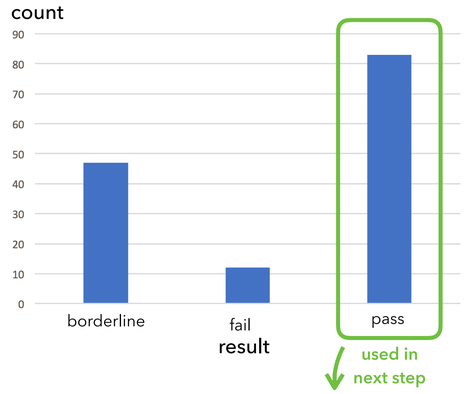


Peak calling results - first sample



Comparison data: We downloaded the call sets from the ENCODE portal (Sloan et al. 2016) (https://www.encodeproject.org/) with the following identifier: ENCBS770TLM

Reproducibility test results



Call reproducible peaks: AD, control

For a given *condition*, where does the histone acetylation occur?

- Used QC metrics from individual peak calling
- 55 high quality samples for AD (6 batches), 29 high quality samples for control (3 batches)
- Pooled sample peaksets into batches - 10 samples each
- Ran pipeline on these batches
- **Output generated:** two peaksets – one for AD, one for control

Summary & Next Steps

Summary

- **Peaks were called** on individual samples
- **QC was performed** to filter out samples w/ reproducible peaks
- **Noise was reduced** in peaksets and overall peaksets were generated

Next Steps

- **Differential peak identification**
  - Where does H3K27ac bind in AD as opposed to control?
- **Differential peak analysis** w/ DESeq2
- Find associated **genes, motifs, pathways**

Future Directions

Which cell types are involved in differential acetylation between AD and control samples?

- **Deconvolve** whole blood data
- **Monocyte profiling** between AD and control samples

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