Assignment 3:

Generate motifs for the top 5 differentially accessible peaks per cell type. From JASPAR, describe their function, and compare them between cell types.

Are the motifs revealing the underlying biology of the different cell types?
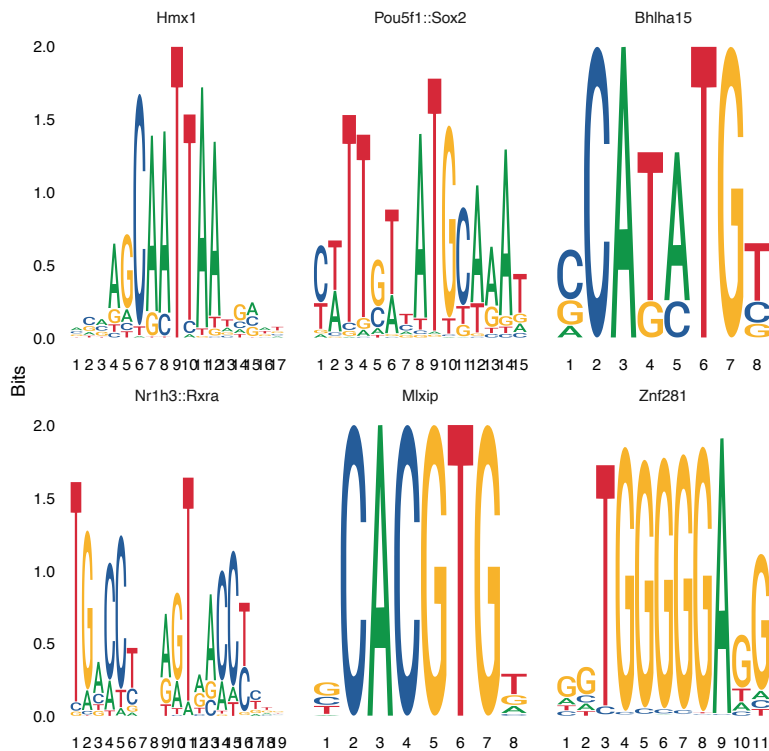
Data: Multiome

Cell types to analyze: Lamp5, Endo, OPC, Pvalb

Differential accessibility test: Wilcoxon test – based on the literature review [1,2]
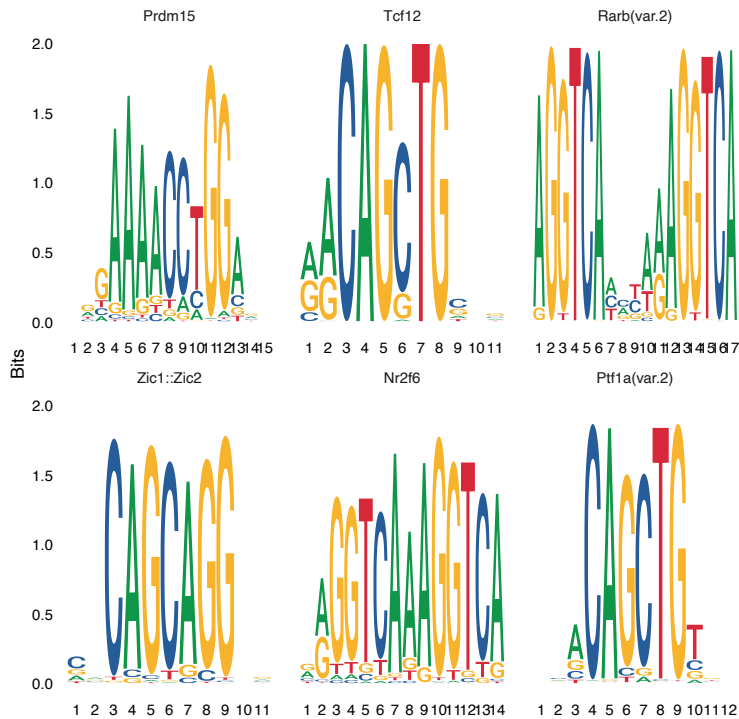
Results:
Transcription factors (TFs) of the enriched motifs within top 5 differential peaks.
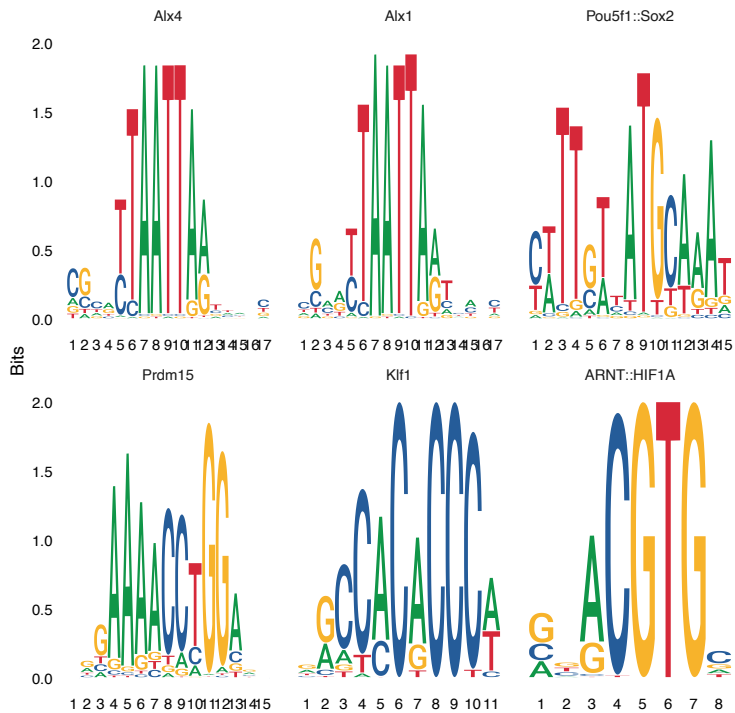
1. Lamp5 cell type that belongs to GABAergic neuron subclasses.

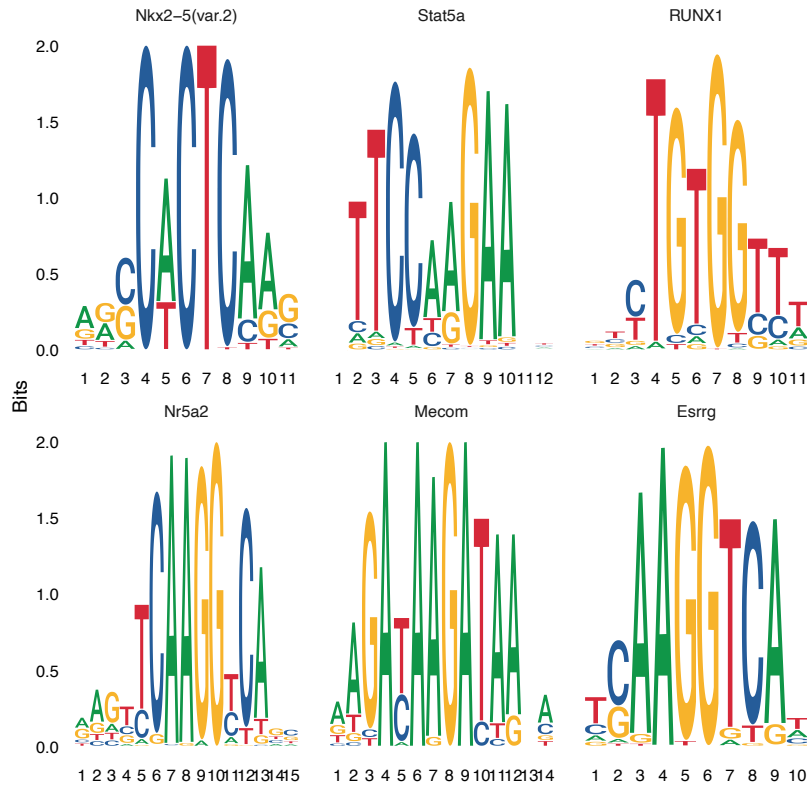2. Pvalb cell type that belongs to GABAergic neuron subclasses.

3. OPC cell type is an oligodendrocyte progenitor cell.

- o Sox2 is expressed in oligodendrocyte progenitor cells (OPCs) preparing to undergo differentiation, allowing them to undergo proliferation and priming them for subsequent differentiation. [3]

4. Endo cell type is an endothelial cell.

- o MECOM has been identified as an endothelial lineage regulator. [4]
- o In human brain endothelial cells, active STAT5 promotes the secretion of prolactin, which stimulates endothelial cell migration and tube formation. [5]

Summary:
The TFs, whose motifs are enriched within top 5 differential peaks are not really specific to any particular cell type. To increase the specificity of the results we could consider analyzing more than just top 5 differential peaks. Additionally, in the initial filtering steps, we could use more strict thresholds. However, it seems that the accessibility itself is not the best modality for the characterization or identification of the cell types. This analysis performed on scRNA-seq data should give more robust results.

References:
[1] Yu W, Uzun Y, Zhu Q, Chen C, Tan K. scATAC-pro: a comprehensive workbench for single-cell chromatin accessibility sequencing data. Genome Biol. 2020 Apr 20;21(1):94. doi: 10.1186/s13059-020-02008-0. PMID: 32312293; PMCID: PMC7169039
[2] Shi P, Nie Y, Yang J, Zhang W, Tang Z, Xu J. Fundamental and practical approaches for single-cell ATAC-seq analysis. aBIOTECH. 2022 Sep 27;3(3):212-223. doi: 10.1007/s42994-022-00082-5. PMID: 36313930; PMCID: PMC9590475.
[3] Zhao C, Ma D, Zawadzka M, Fancy SP, Elis-Williams L, Bouvier G, Stockley JH, de Castro GM, Wang B, Jacobs S, Casaccia P, Franklin RJ. Sox2 Sustains Recruitment of Oligodendrocyte Progenitor Cells following CNS Demyelination and Primes Them for

Differentiation during Remyelination. J Neurosci. 2015 Aug 19;35(33):11482-99. doi: 10.1523/JNEUROSCI.3655-14.2015. Erratum in: J Neurosci. 2017 Sep 20;37(38):9345. PMID: 26290228; PMCID: PMC6605237.

[4] Lv, J., Meng, S., Gu, Q. et al. Epigenetic landscape reveals MECOM as an endothelial lineage regulator. Nat Commun 14, 2390 (2023). https://doi.org/10.1038/s41467-023-38002-w

[5] Yang X, Meyer K, Friedl A. STAT5 and prolactin participate in a positive autocrine feedback loop that promotes angiogenesis. J Biol Chem. 2013 Jul 19;288(29):21184-21196. doi: 10.1074/jbc.M113.481119. Epub 2013 Jun 2. PMID: 23729680; PMCID: PMC3774384.