

## Introduction

5.8 million people in the U.S currently have dementia. Dementia is a broad term referring to a loss of cognitive functioning, primarily thinking and memory.

### Three Most Common Types of Dementia

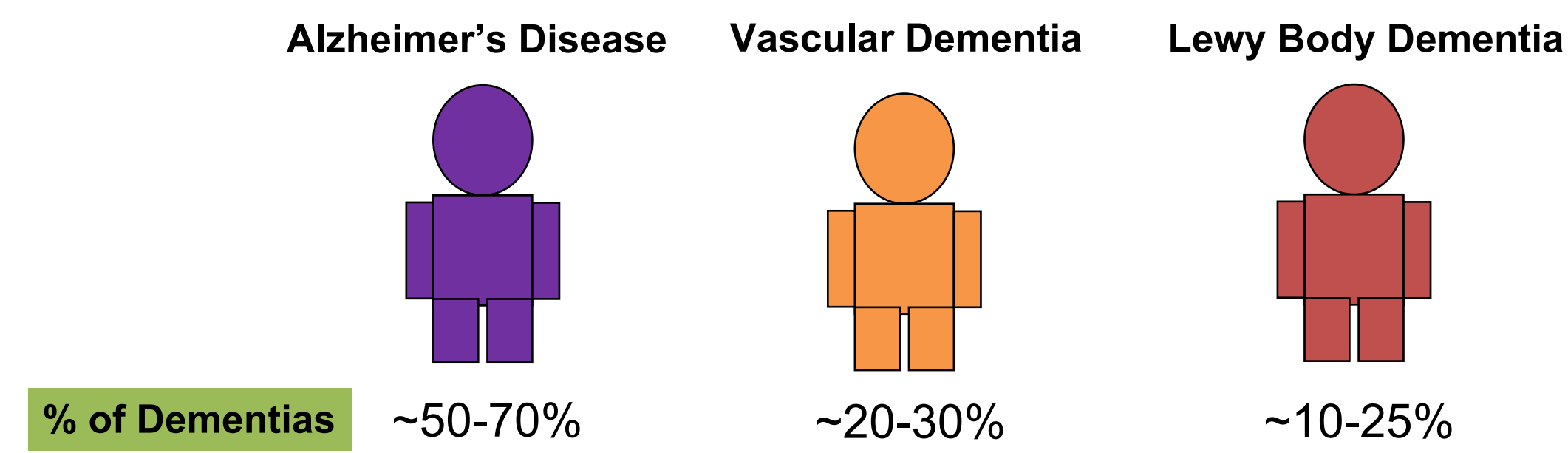


Figure 1: Common types of dementia with frequency estimates.

### How do brain cells act differently between dementia types?

We hypothesized that differences in cell function between dementia types could be detected from single nuclei RNA sequencing (sn-RNAseq) and be used to gain insight into dementia specific mechanisms.

## Methods

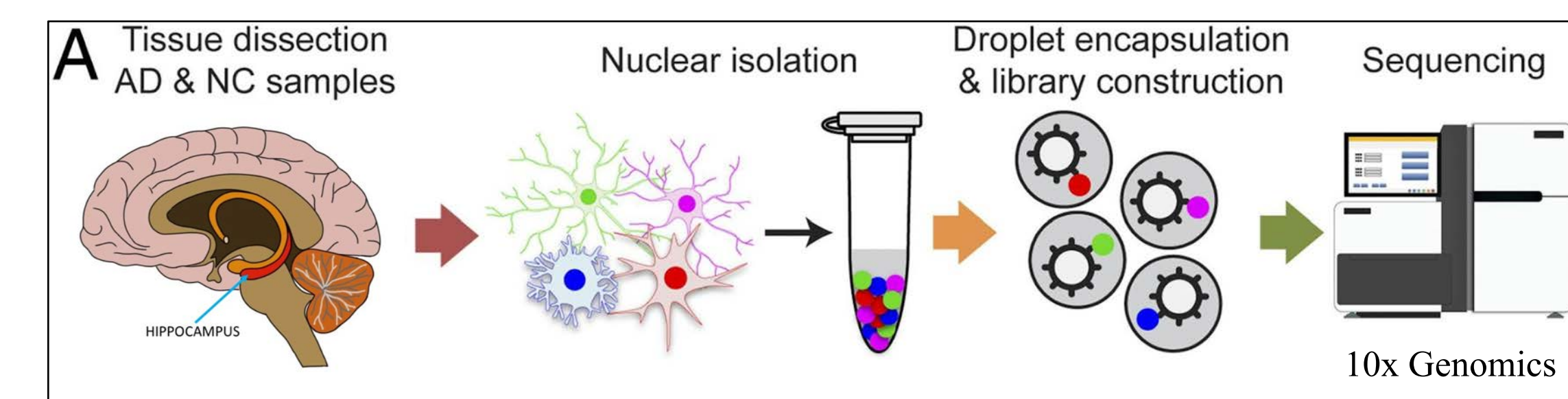
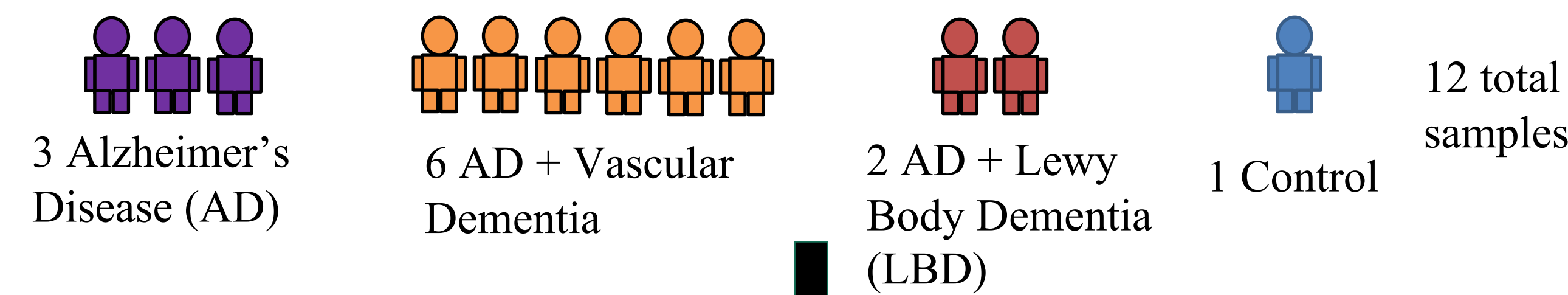
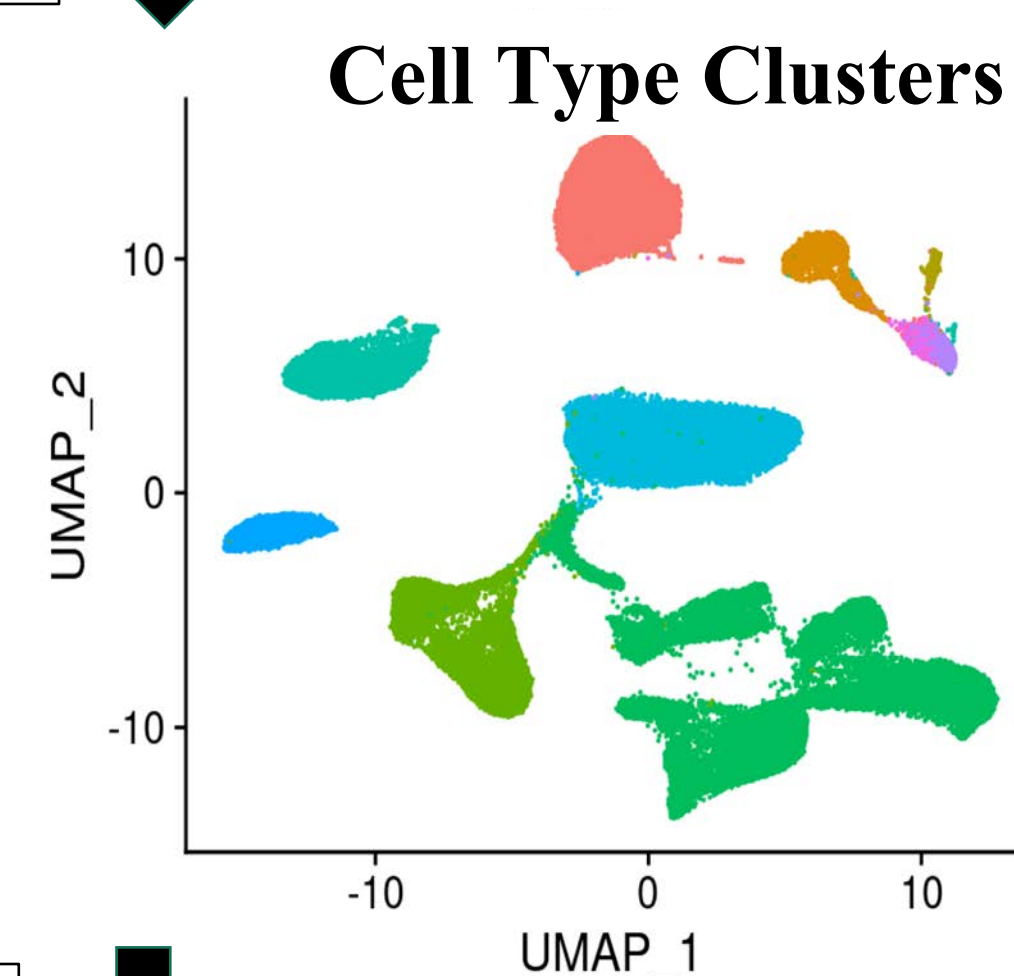


Figure 2: Representation of hippocampus tissue dissection and single nuclei RNA sequencing. NC stands for normal control. Adapted from (Lau et al., 2020).

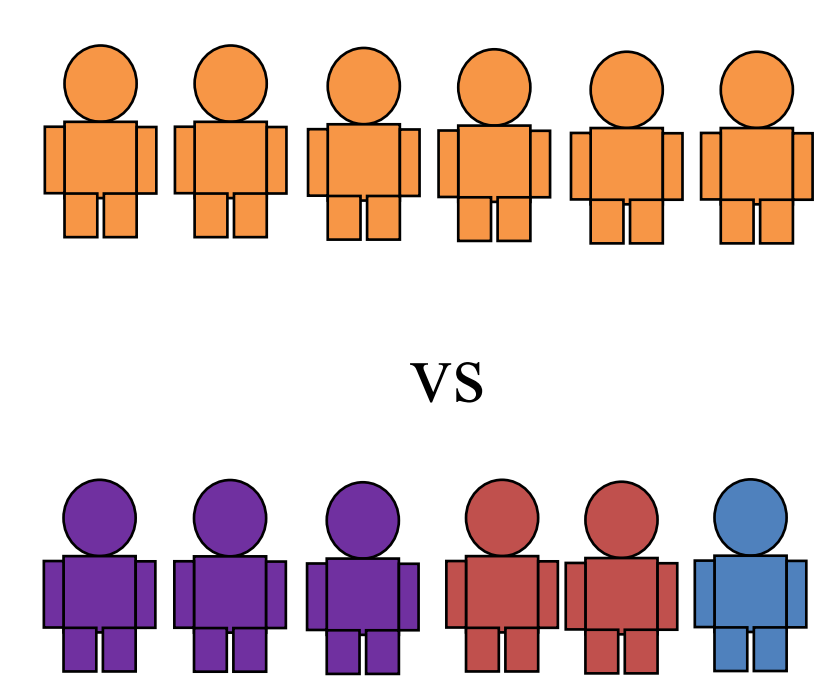
### Quality Control

- Cell Clustering**
- Groups cells into clusters based on similar gene expression
  - Allows identification of cell type

- Quality Control Metrics**
- 76.2% of original cells passed quality control
  - Identified 79,944 cells across 11 cell types



### Differential Gene Expression



Alzheimer's Disease + Vascular Dementia (Mixed Dementia)

Remaining Samples

## Results

Evidence suggests this cluster of 128 cells consists of endothelial cells responding to vascular calcification and is specific to vascular dementia

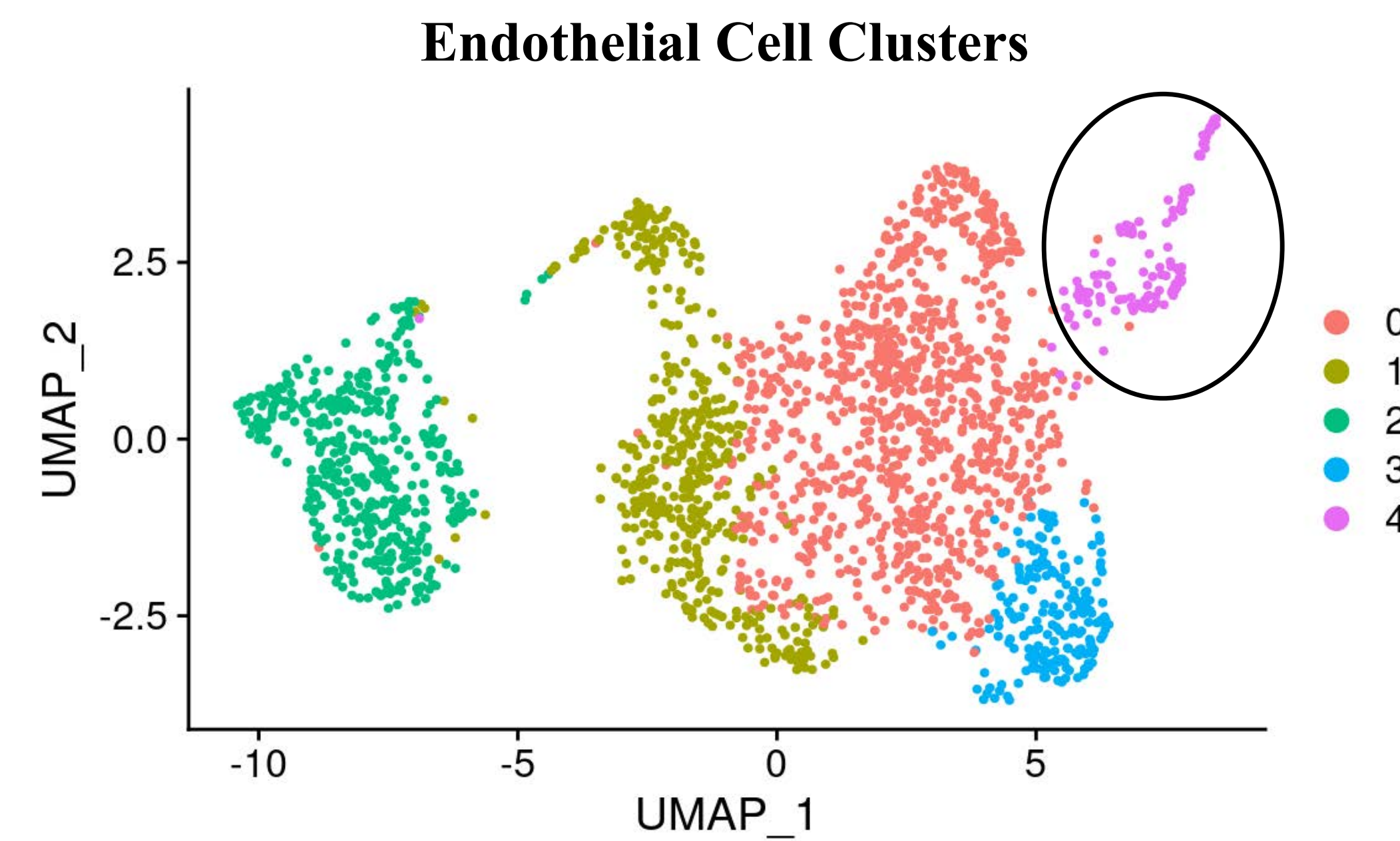


Figure 3: UMAP of endothelial cell type clustering. Cluster 4 is composed of 128 cells where 90% are from the six Alzheimer's Disease + Vascular Dementia samples.

### Percent of Sample's Endothelial Cells in Cluster 4

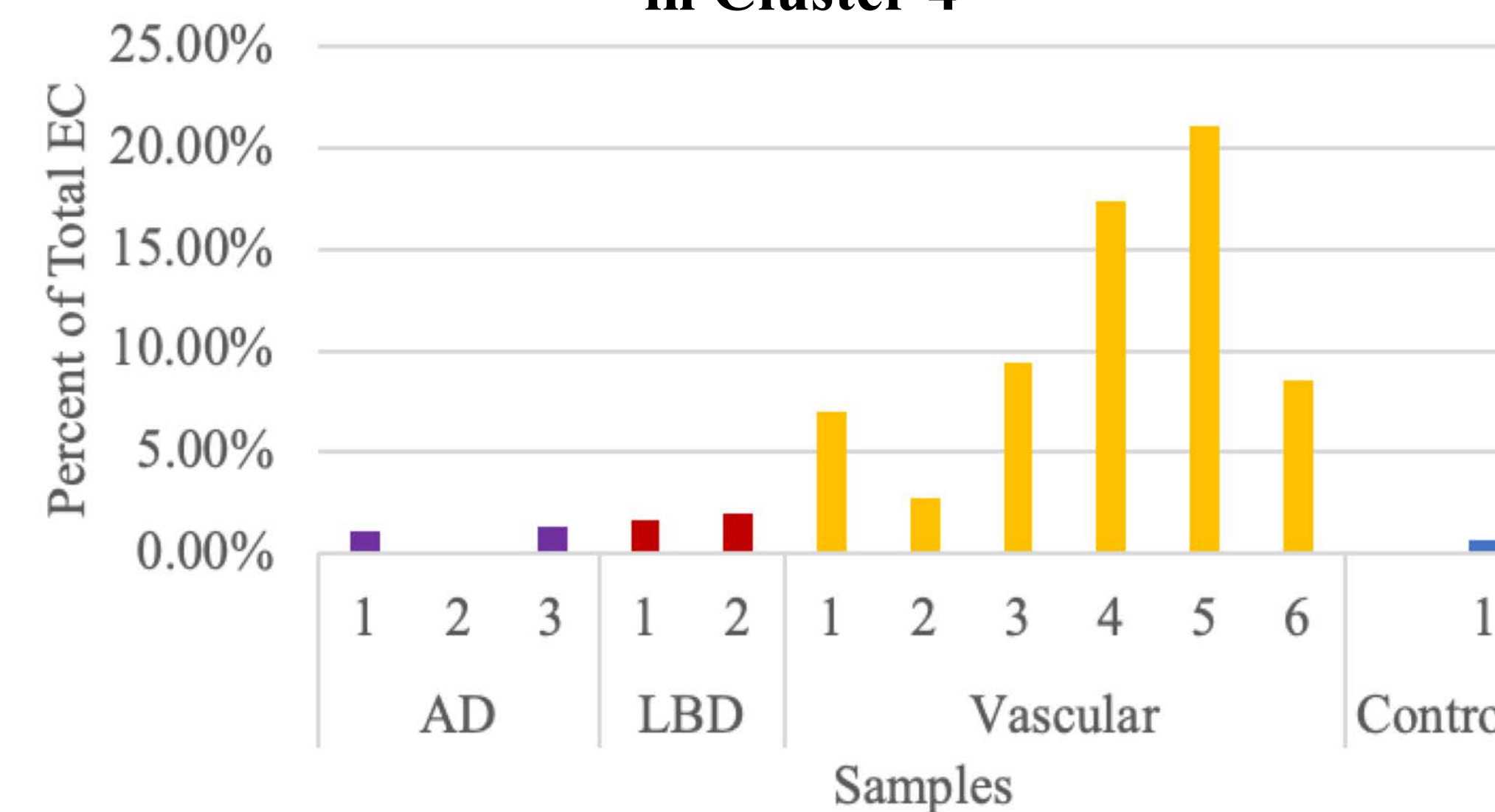


Figure 4: Bar graph depicting the percentage of each sample's endothelial cells in cluster 4. Percentage ranged from 2.7% to 21.1% of endothelial cells in vascular dementia samples with an average of 11.5%.

### MGP and DKK2 Average Expression in Endothelial Cell Clusters

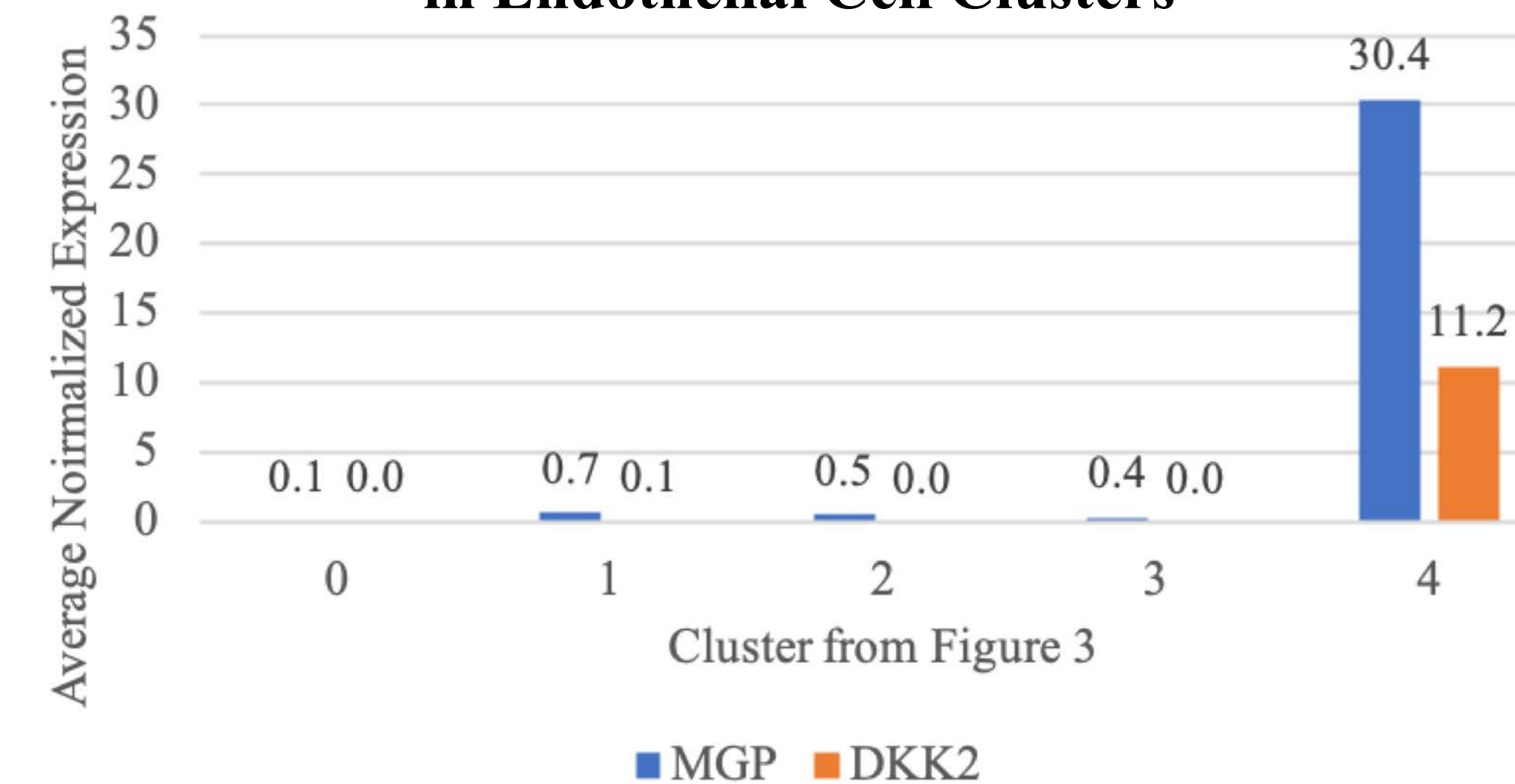


Figure 5: Average gene expression graphs for two highly upregulated genes in cluster 4 related to vascular calcification. Matrix Gla Protein (*MGP*) is a primary inhibitor of vascular calcification. Dickkopf WNT Pathway Inhibitor 2 (*DKK2*) is part of the WNT/ $\beta$  catenin signaling pathway which promotes calcification (Bundy, Boone and Simpson, 2021).

## Vascular Calcification

- Vascular calcification describes the build-up of minerals along blood vessel walls.
- Can lead to decreased blood flow, one of the primary causes of vascular dementia.
- Brain vascular calcification is poorly characterized.
- MGP* is a vitamin K2 dependent protein that disrupts calcium deposition, serving as a primary inhibitor of vascular calcification (Jaminon et al., 2020)

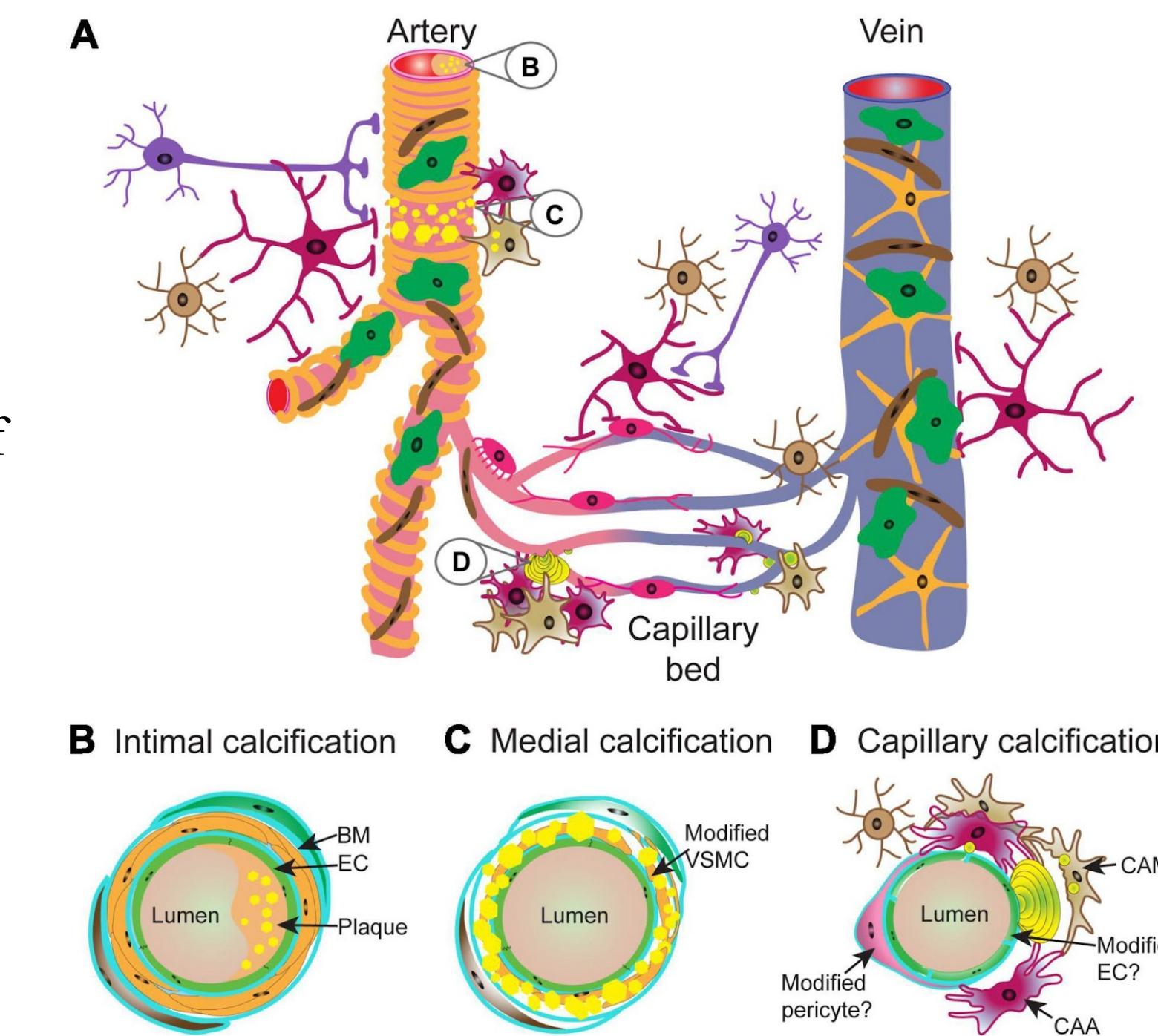


Figure 6: Types of vascular calcification in the Central Nervous System. Impact of vascular calcification on endothelial cells is especially poorly characterized. (Maheshwari et al., 2022).

## Conclusion and Future Work

### Possible Connection

Brain capillary calcification

Vascular dementia progression

- Evidence suggests we have identified brain hippocampus endothelial cells responding to vascular calcification in vascular dementia.
- These cells highly upregulate genes *MGP* (23-fold increase) and *DKK2* (12-fold increase). These two genes are related to calcification response, with *MGP* being the primary inhibitor of vascular calcification within the human body.
- Future work would aim to confirm whether these cells are responding to vascular calcification and explore how calcification contributes to dementia symptoms. The roles of *MGP* and *DKK2* in dementia progression will also be investigated.

## References and Acknowledgements

Bundy, K., Boone, J. and Simpson, C., 2021. Wnt Signaling in Vascular Calcification. *Frontiers in Cardiovascular Medicine*, 8, 708470. <https://doi.org/10.3389/fcvm.2021.708470>

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Yang, A., Vest, R., Kern, F., Lee, D., Agam, M., & Maat, C. et al. (2022). A human brain vascular atlas reveals diverse mediators of Alzheimer's risk. *Nature*, 603(7903), 885-892. <https://doi.org/10.1038/s41586-021-04369-3>

This work was funded, in part, by NSF grant DBI-1949968, awarded to the Boston University Bioinformatics BRITE REU program

Thank you to Dr. Gary Benson, Dr. Xiaoling Zhang, Nick O'Neill, and Boston University Bioinformatics for their help and mentorship.