

Spatially Resolved Cell-Type-Specific Molecular Drivers of Anterior Temporal Pole Neuropathology in FTLD-TDP Type C

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Abstract

Frontotemporal lobar degeneration (FTLD) with TDP-43 Type C pathology (TDP-C) is characterized by pronounced unilateral anterior temporal lobe (ATL) atrophy and colocalization of phosphorylated TDP-43 (pTDP-43) and annexin A11 (ANXA11) aggregates in predominantly long, tortuous dystrophic neurites (DN) in superficial cortical laminae (cortical layers I/II/III). Clinically, TDP-C originating in the right ATL primarily presents with behavioral variant FTD (bvFTD), but primary progressive aphasia (PPA) when originating in the left ATL. The molecular basis for selective ATL vulnerability, hemispheric asymmetry, and regional disease spread remains poorly understood.

We integrated spatial transcriptomics (ST) with single-cell RNA sequencing (scRNAseq) to define region- and cell-type specific transcriptomic alterations in TDP-C. Formalin-fixed paraffin-embedded (FFPE) tissue from paired left and right ATL, inferior frontal gyrus (IFG), and middle frontal gyrus (MFG) was analyzed from six pathologically confirmed TDP-C cases with svPPA and five non-neurological disease (NND) controls. Immunofluorescence was used to assess regional proteinopathy.

The left ATL exhibited the most significant transcriptomic dysregulation, accounting for the vast majority of differentially expressed genes (DEGs) identified. Minimal hemispheric asymmetry in controls indicated disease-specific left ATL vulnerability. Compared to NND, the left ATL showed marked dysregulation in smooth muscle cells, arterial endothelial cells, microglia, and inflammatory astrocytes. Within TDP-C, interneuron dysregulation uniquely distinguished the ATL from frontal regions. Transcriptomic alterations decreased with distance from the ATL (ATL > IFG > MFG), consistent with a spatial gradient of pathology. Outside the left ATL, transcriptomic changes correlated with pTDP-43-ANXA11 aggregation in cortical layers I/II/III. Functional enrichment analyses highlighted neurovascular dysfunction and innate immune activation.

These findings suggest that selective vulnerability of ATL interneurons projecting to superficial cortical layers underlies characteristic TDP-C proteinopathy and regional disease onset. Moreover, the left ATL exhibits distinct transcriptomic features that confer preferential vulnerability to TDP-C with svPPA. Widespread neurovascular and immune-related transcriptomic changes further implicate blood-brain barrier disruption and neuroinflammation in TDP-C initiation and progression.

Background

In-vivo staging of FTLD-TDP Type C:
Areas Atrophied in All Cohort Patients

Right Inferior Parietal Lobe
Spared Atrophy

Left Anterior Temporal Lobe
Pronounced Atrophy

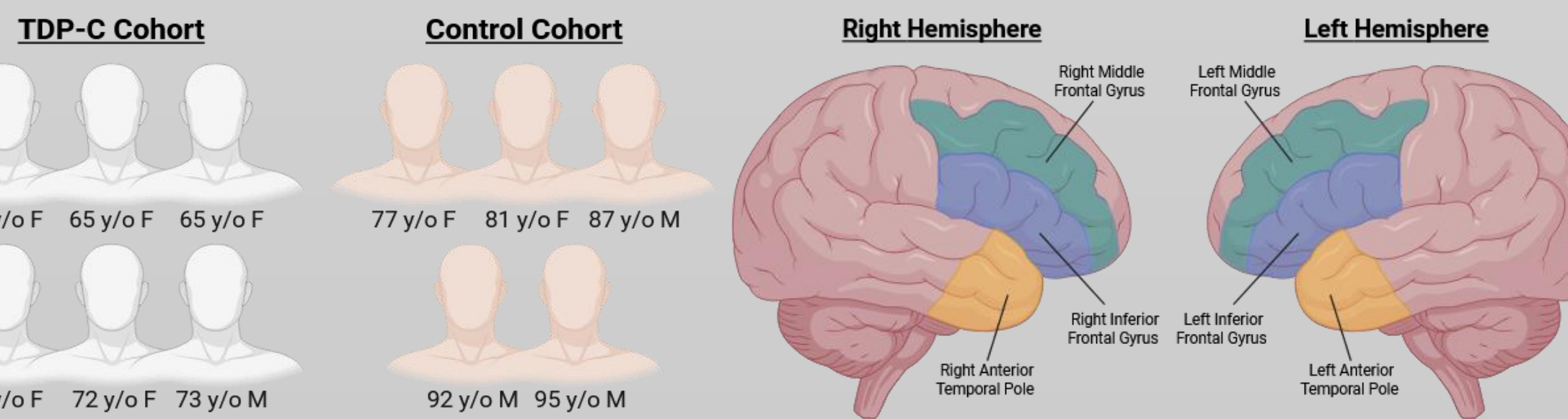
TDP-43 IHC +
Cresyl Violet Counterstain

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Methodology – Cohort Design

Cohort Patient Breakdown

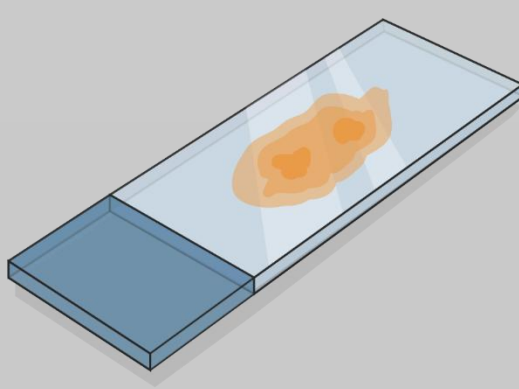
Region Samples Taken From Each Brain



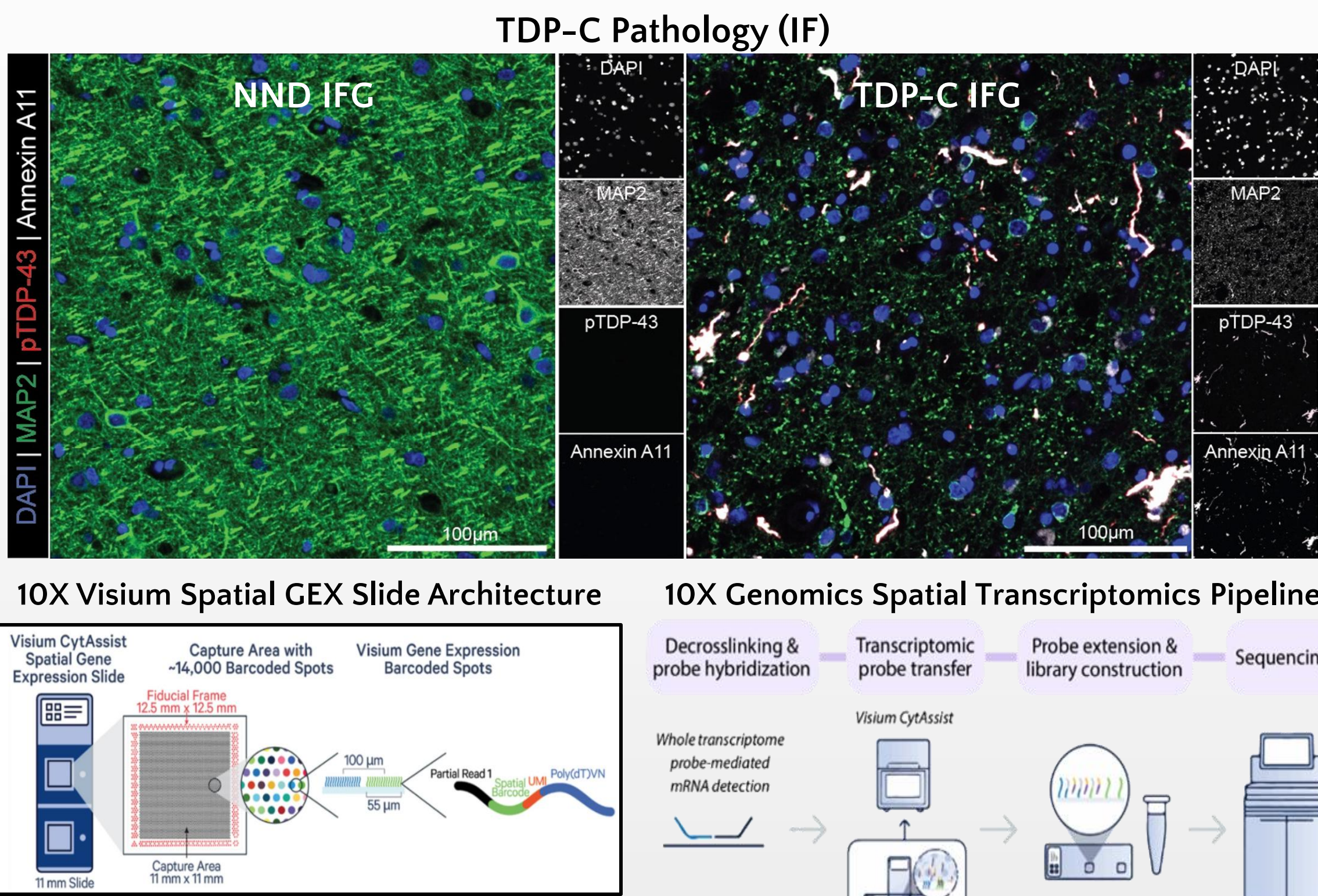
Cohort Demographics Table

Characteristic	Left, N = 28			Right, N = 32		
	Inferior Frontal Gyrus N = 10 ^a	Middle Frontal Gyrus N = 9 ^a	Temporal Pole N = 9 ^a	Inferior Frontal Gyrus N = 10 ^a	Middle Frontal Gyrus N = 11 ^a	Temporal Pole N = 11 ^a
Donor Demographics						
Sex						
Female	6 (60%)	6 (67%)	6 (67%)	6 (60%)	7 (64%)	7 (64%)
Male	4 (40%)	3 (33%)	3 (33%)	4 (40%)	4 (36%)	4 (36%)
Age	75 (66, 87)	77 (66, 87)	77 (66, 87)	75 (66, 87)	73 (65, 87)	73 (65, 87)
Dx						
Normal Control	5 (50%)	5 (56%)	5 (56%)	5 (50%)	5 (45%)	5 (45%)
TDP Type C	5 (50%)	4 (44%)	4 (44%)	5 (50%)	6 (55%)	6 (55%)

Formalin-Fixed
Paraffin Embedded
(FFPE) Slides

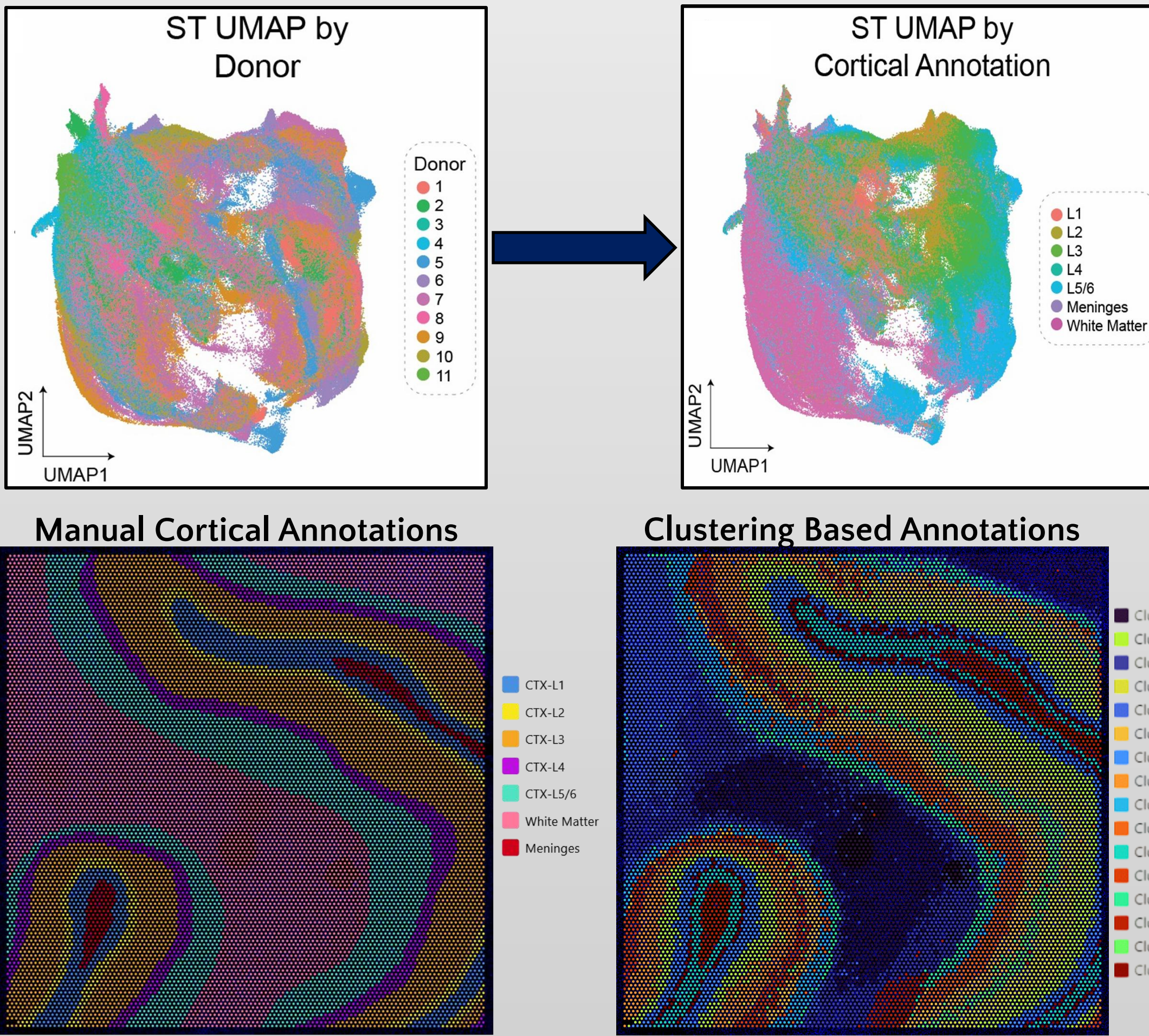


Methodology – Spatial Transcriptomics

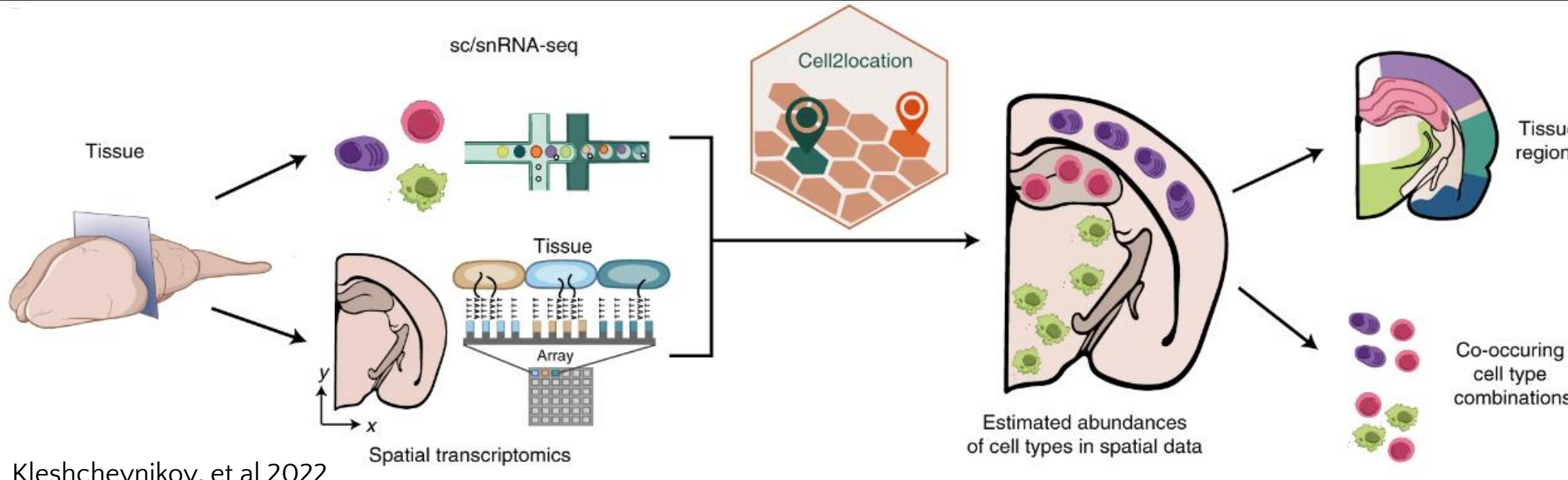


Methodology - Computational

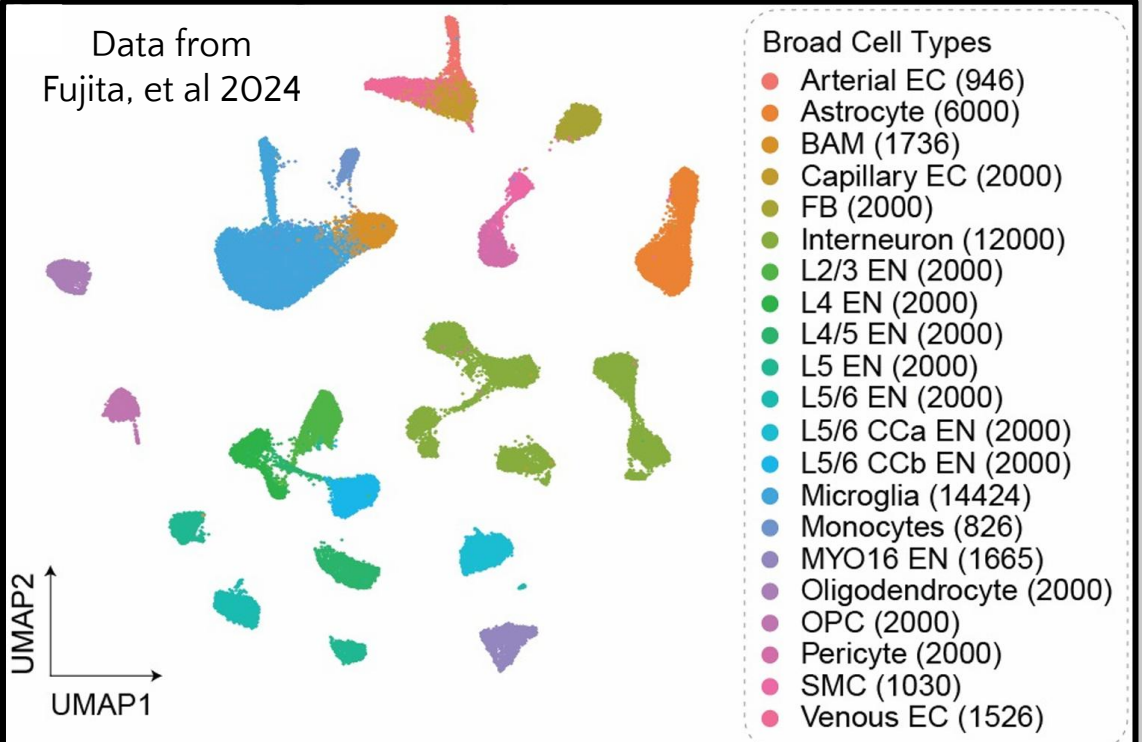
Harmony Integration by of ST Spots by Donor and Manual Cortical Annotations



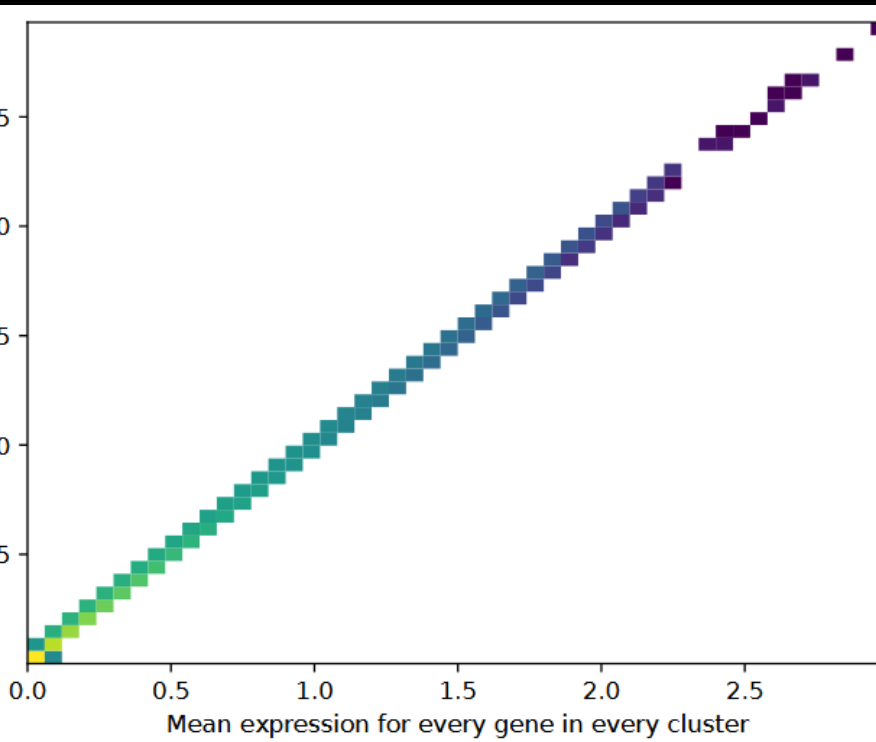
Cell2Location Cell Type Deconvolution of ST Spots



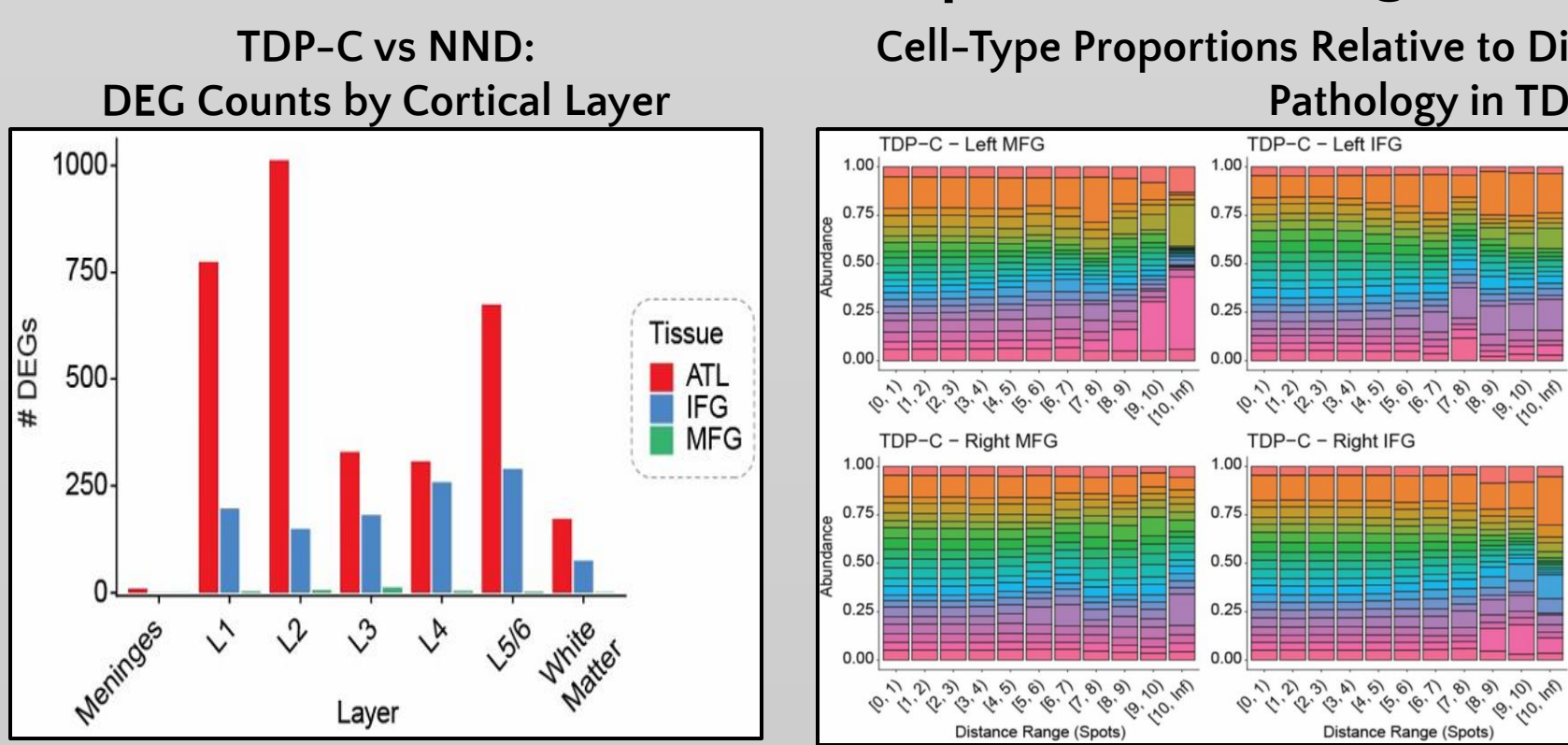
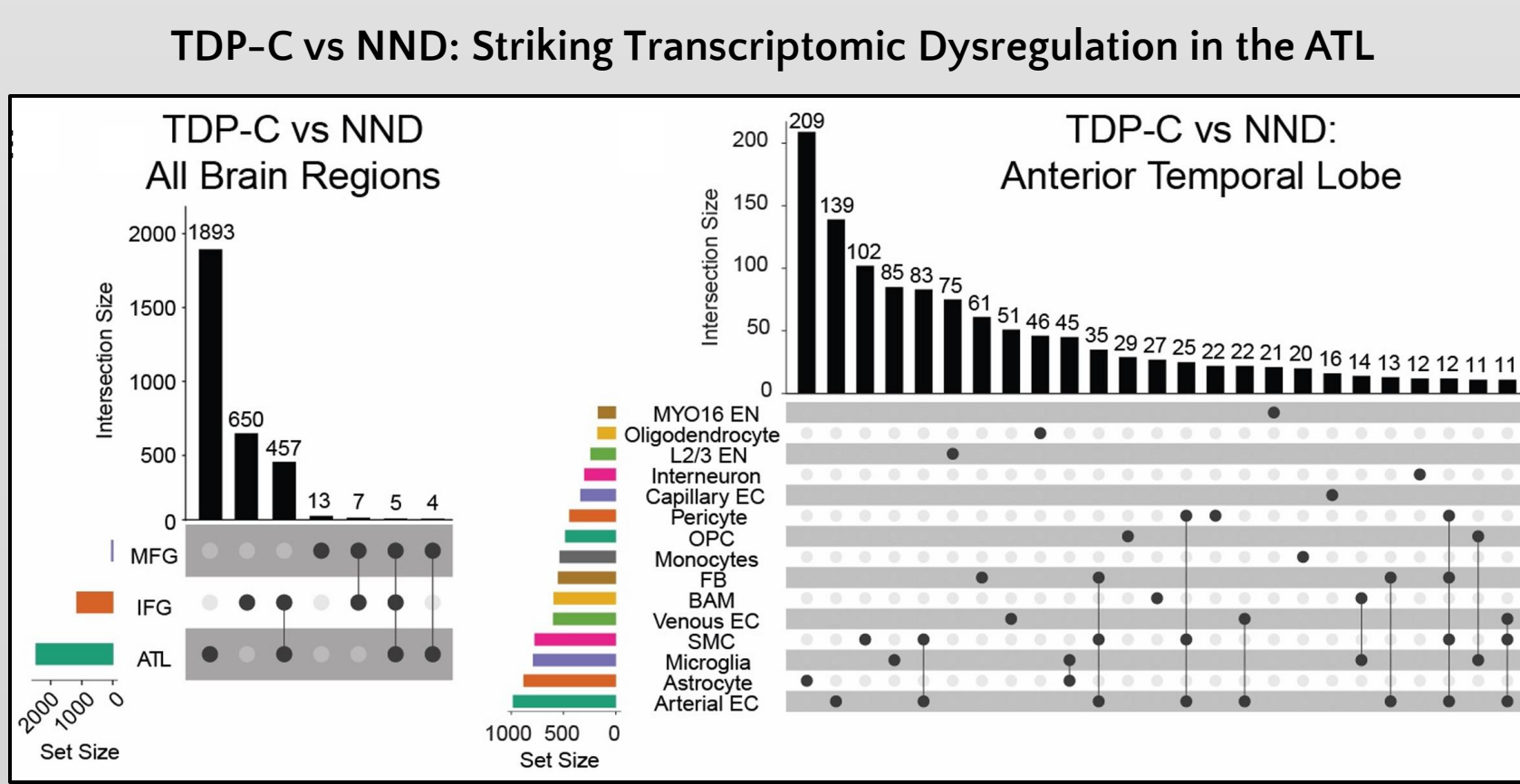
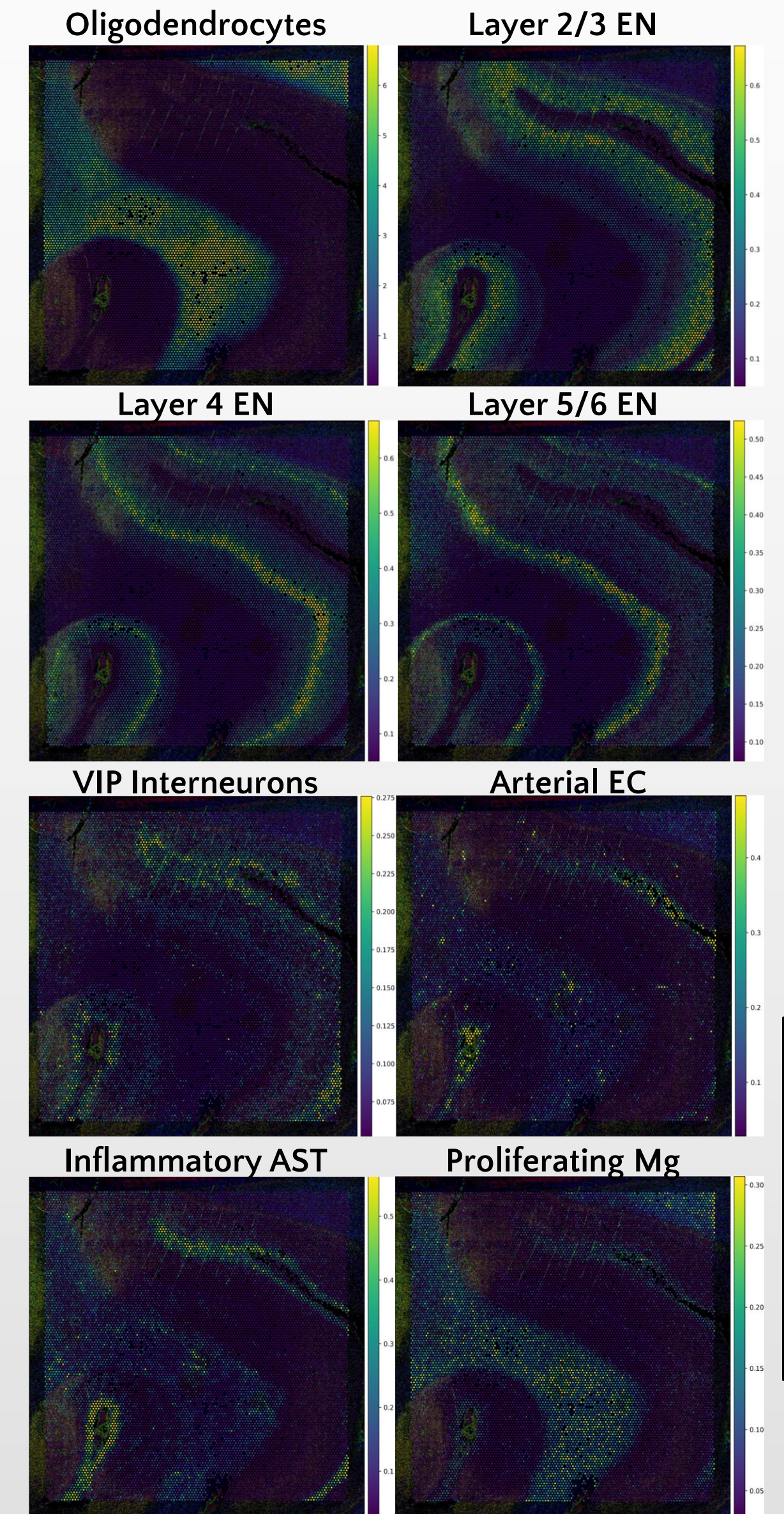
ROSMAP Spatial Deconvolution Reference



Cell2Location Model Training



Cell2Location Spatial Deconvolution Enables
High Resolution Cellular Tissue Mapping



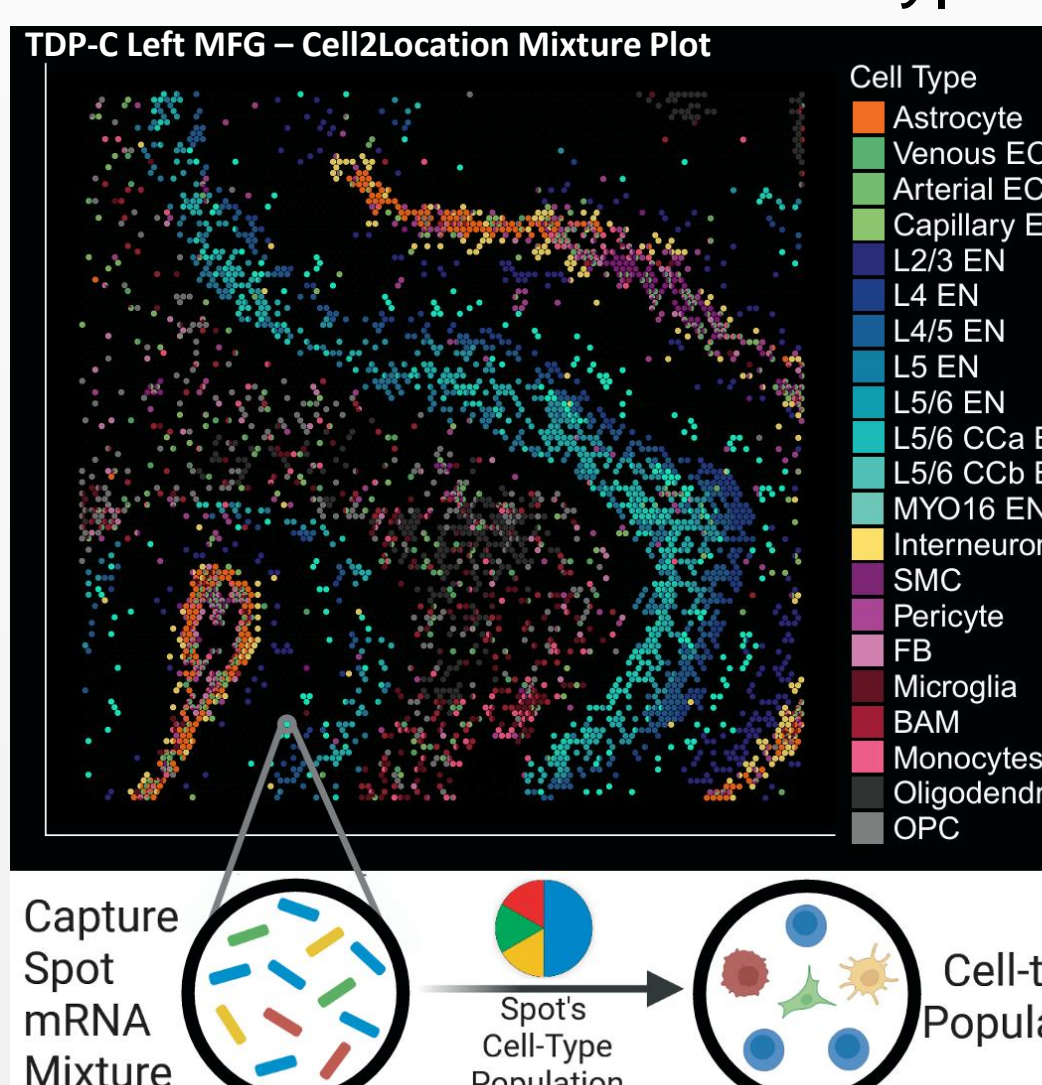
Explore Our Data!

Scan to View Interactive Web Applications!

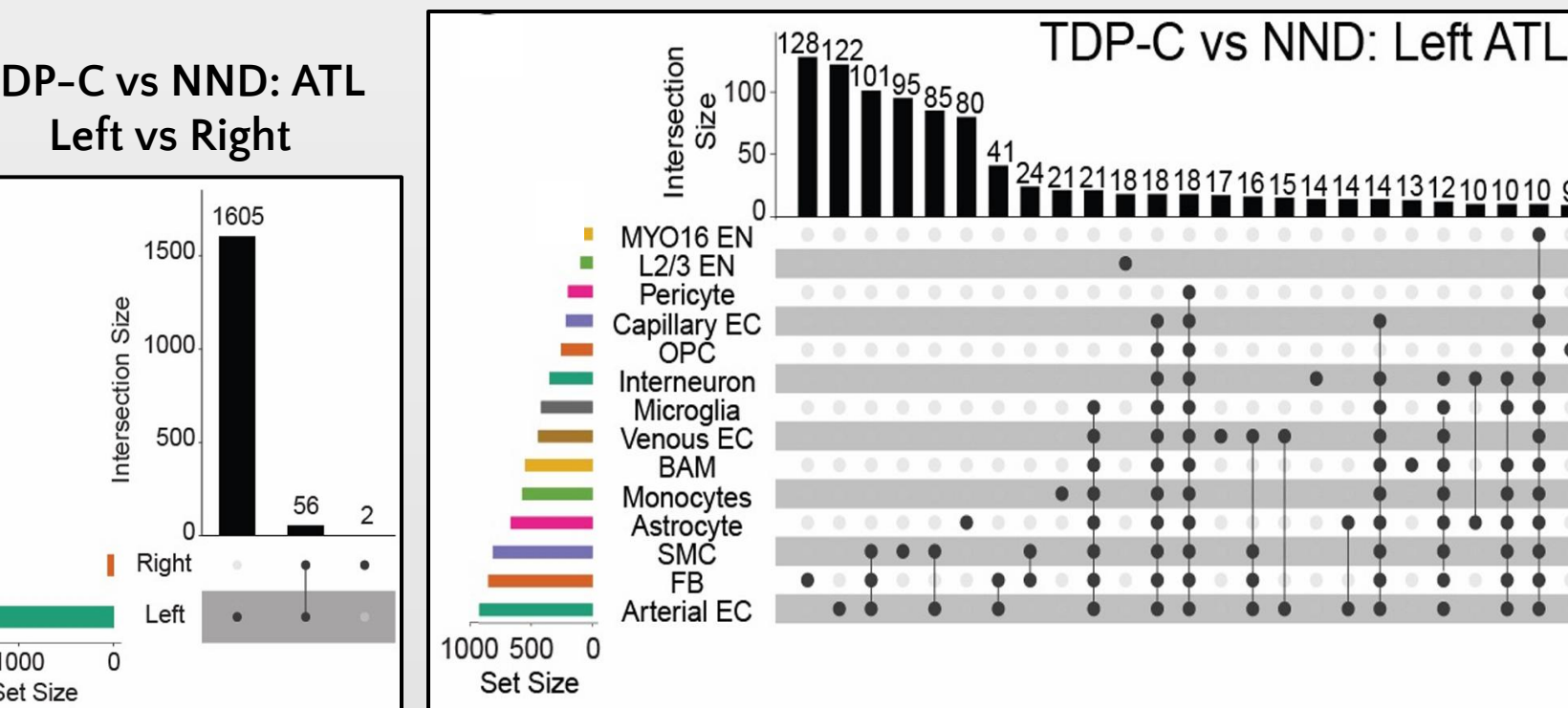


Results

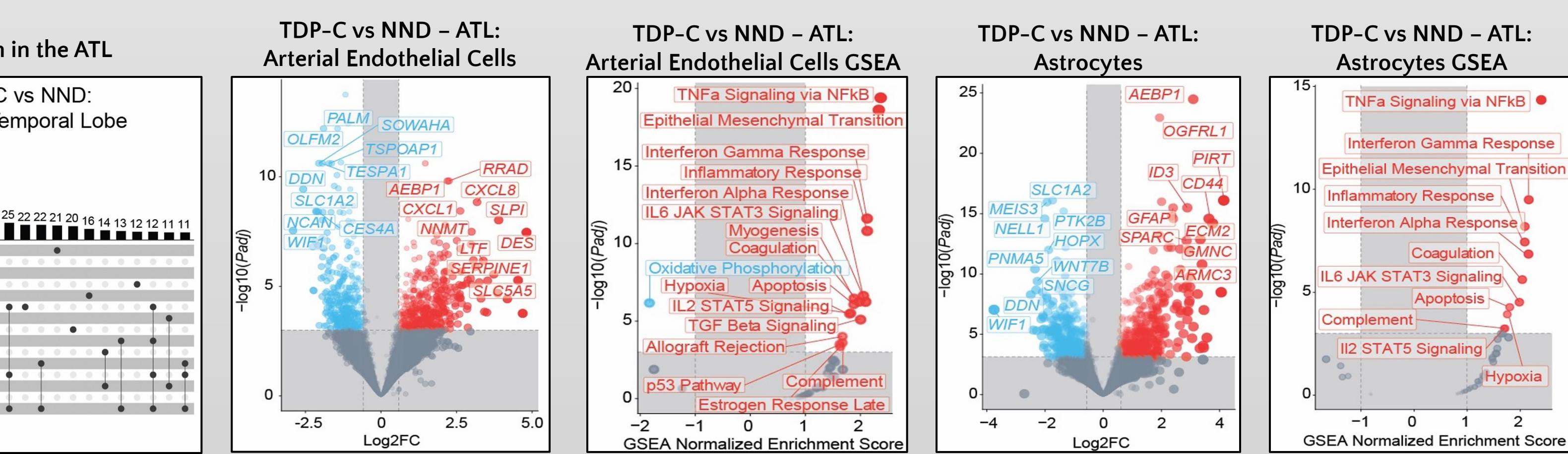
Differential Expression in
Cell2Location-Derived Cell Types



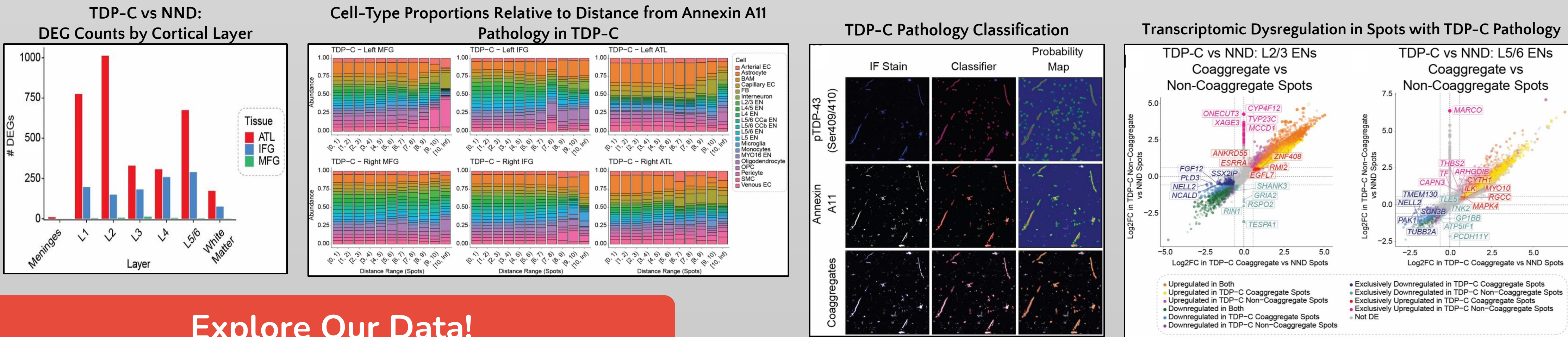
TDP-C vs NND: Stratification Reveals Dominant Left Hemisphere Dysregulation



Loss of Regional Transcriptonal Identity in TDP-C Anterior Temporal Pole



Laminar and Spatial Convergence of pTDP-43-ANXA11 Pathology with Transcriptomic Dysregulation



References

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- Kleshchevnikov, V., Shmatko, A., Dann, E. et al. Cell2location maps fine-grained cell types in spatial transcriptomics. Nat Biotechnol 40, 661–671 (2022). <https://doi.org/10.1038/s41587-021-01139-4>
- Fujita, M., Gao, Z., Zeng, L. et al. Cell subtype-specific effects of genetic variation in the Alzheimer's disease brain. Nat Genet 56, 605–614 (2024). <https://doi.org/10.1038/s41588-024-01685-y>