

L5ET neurons show distinct yet overlapping gene expression profiles in ACC, FI, PreCG and V1

Felipe Pereira, William Seeley

State of the art. Layer 5 subcerebral/extratelencephalic projection neurons (L5ET) comprise von Economo (VENs), Betz, fork and pyramidal cells, and others in a conserved and distributed neuronal class. These L5ET neurons includes subclasses FLTD-vulnerable and -resistant. While VENs and fork cells are vulnerable to tau and TDP-43, the upper motor neurons, such as Betz, in precentral gyrus (PreCG) are only selective vulnerable to TDP-43. Meynert cells, also L5ET neurons, are not vulnerable for both, tau and TDP-43, in primary visual cortex. Despite this knowledge, little is known about the regional gene signature and expression profile of these cells.

Methodology. To access regionally specialized transcriptomic profile we explored regional single nucleus RNAseq (snRNAseq) data from anterior cingulate cortex (ACC), Frontoininsula (FI), PreCG, primary visual area (V1), and other cortical areas not early targeted in FTLN-tau or FTLN-TDP. All snRNAseq data from different dataset were normalized using log count per million and aligned using Seurat 4.1 and Harmony libraries on R software.

Results. We found 662 genes expressed uniquely in L5ET neurons from ACC and FI, including known VENs markers, whereas 411 genes were shared among ACC, FI, and PreCG but not expressed in other L5ET neurons. Gene-ontology term analyses nominated distinct vulnerability pathways ($p < 0.05$) for tau (DNA damage, macroautophagy, others) and TDP-43 (mitochondrial biosynthesis, innate immunity, others).

Conclusion. Now, we want to refine and extend this analysis, including other cortical areas (e.g., primary motor cortex) and validating these discoveries using quantitative histopathological assessment with multiplex immunofluorescence.

Conflicts of interest

N/A