Counterfactual Confounder Adjustment for Single-cell Differential Expression Analysis

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Results

Cell type annotation

2,648 marker genes

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PsychENCODE's marker gene selection might be imperfect since some "marker" genes are shared by different cell types. However, it has enough discriminatory power. Using this initial dictionary of marker genes, we can start analyzing 10x data, which consist of these three files:

- Sparse count matrix:

```
## %%MatrixMarket matrix coordinate integer general
## 17926 70634 119696200
## 56 1 1
## 139 1 1
## 270 1 1
## 324 1 1
## 375 1 1
## 389 1 1
## 420 1 1
## 557 1 1
```

- Cell barcode list:

```
## AAACGGGAGATCCCGC.1
## AAATGCCTCCAATGGT.1
## AACCATGTCAGTGCAT.1
## AACCATGTCTGTACGA.1
## AACCGCGTCCGCATAA.1
## AACGTTGGTTCAGGCC.1
## AACTGGTGTACCGGCT.1
## AAGACCTAGTTAACGA.1
## AAGGAGCAGCAATCTC.1
## AAGGAGCTCTGCTGCT.1
```
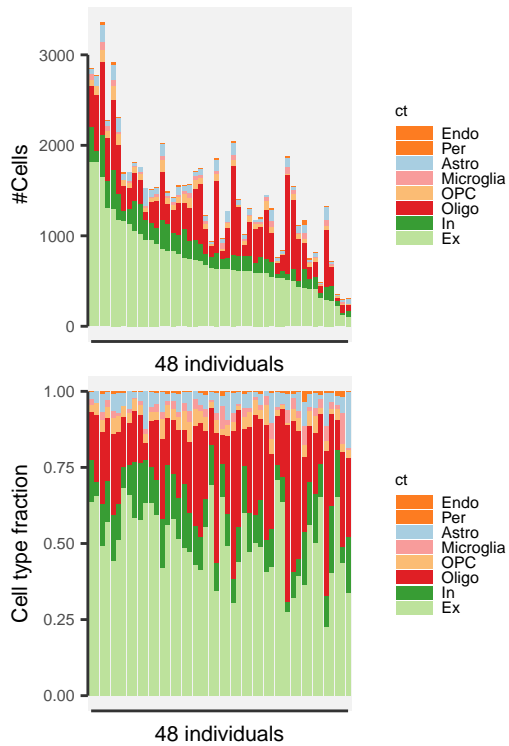
- Gene/feature list (**these names should exist in the marker file**):

```
## F0538757.2
## SAMD11
## NOC2L
## KLHL17
## PLEKHN1
## PERM1
## HES4
## ISG15
## AGRN
## RNF223
```


1726 genes present in snRNA−seq
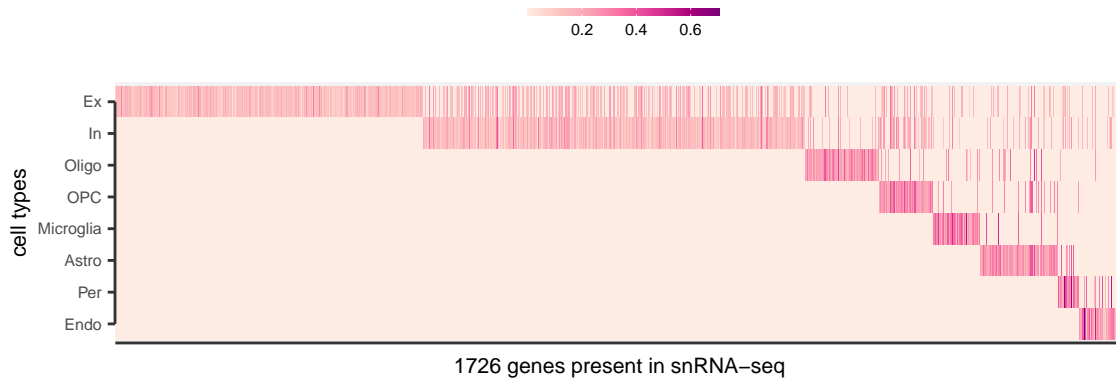
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Basic statistics for cell type annotation

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- 1,472 cells per individual, including 50.9% (N=745 ± 388) cells for Ex, 12.23% (N=179 ± 103) cells for In, 3.54% (N= 54 ± 35) cells for OPC, 0.33% (N= 4 ± 5) cells for Endo, 25.22% (N=380 ± 252) cells for Oligo, 2.61% (N= 36 ± 25) cells for Microglia, 4.95% (N= 71 ± 47) cells for Astro, 0.34% (N= 4 ± 4) cells for Per on average.

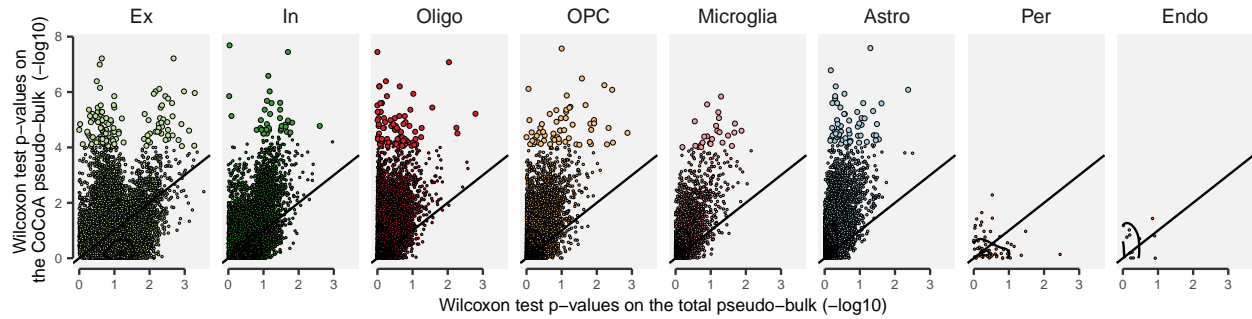## Differential expression analysis

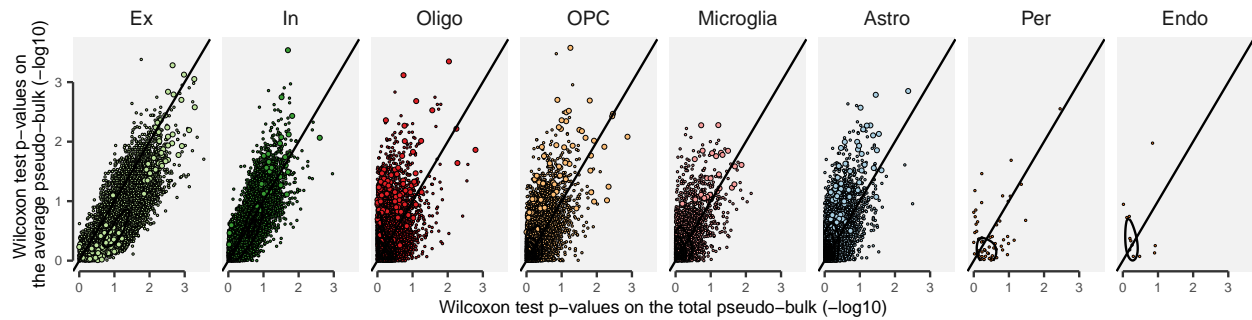### CoCoA identified 377 genes are differentially-regulated between different AD conditions

- 377 genes (2.72%) consist of 123 found in Ex, 36 found in In, 86 found in Oligo, 58 found in OPC, 24 found in Microglia, 57 found in Astro
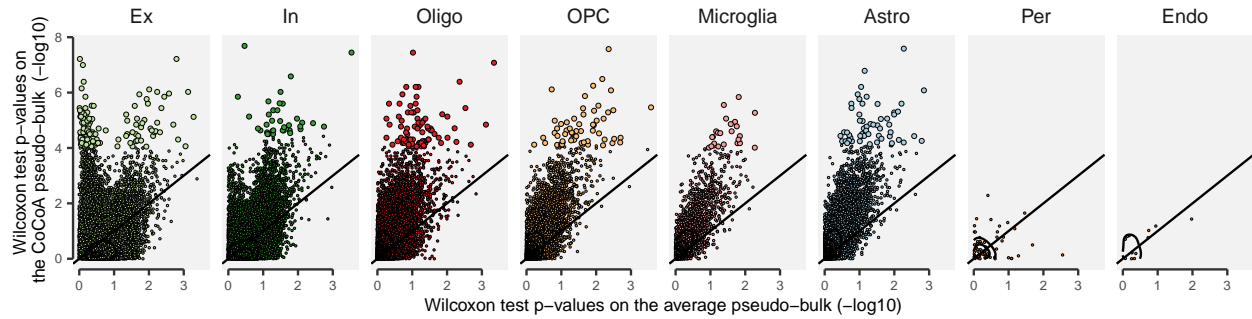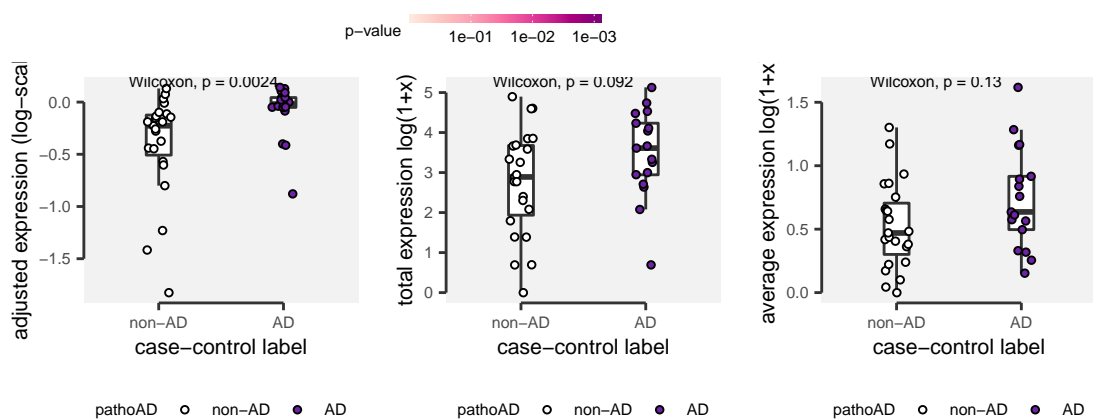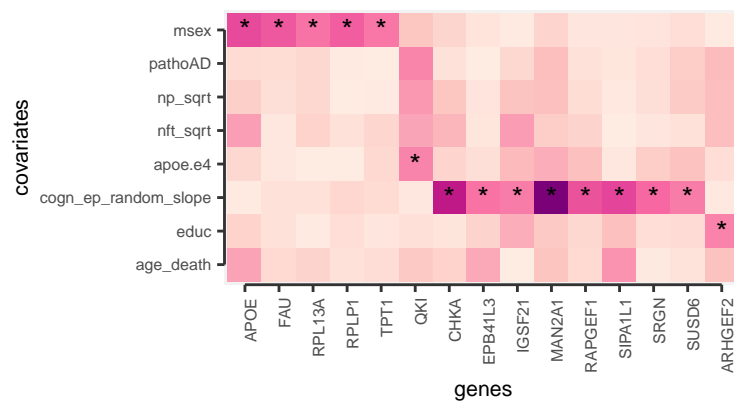

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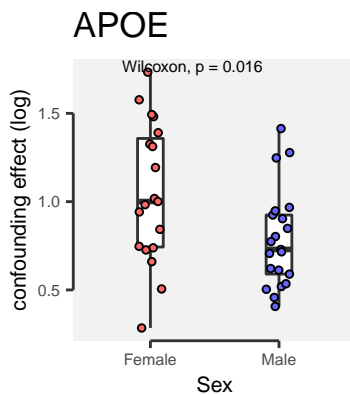
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```
## pdf
##   2
```

p-value distribution

Why do we find more genes with CoCoA?
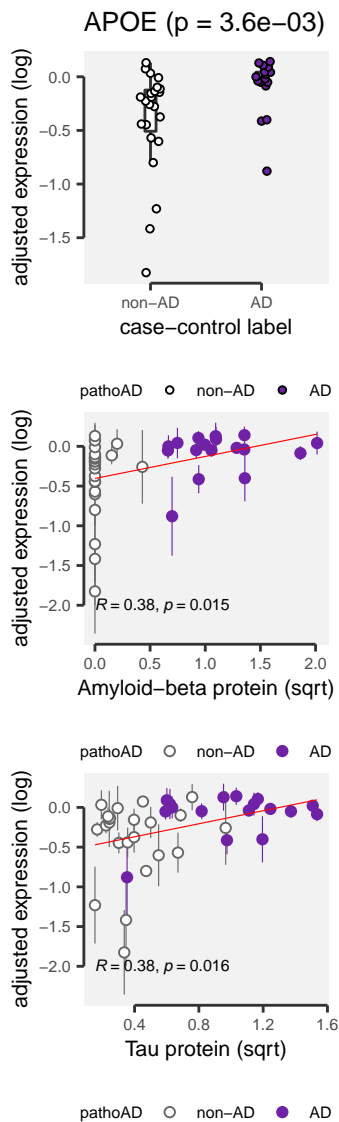
Take the examples of Microglia genes

```
## Loading required package: cba

## Loading required package: proxy

##
## Attaching package: 'proxy'

## The following objects are masked from 'package:stats':
##
##       as.dist, dist

## The following object is masked from 'package:base':
##
##       as.matrix
```
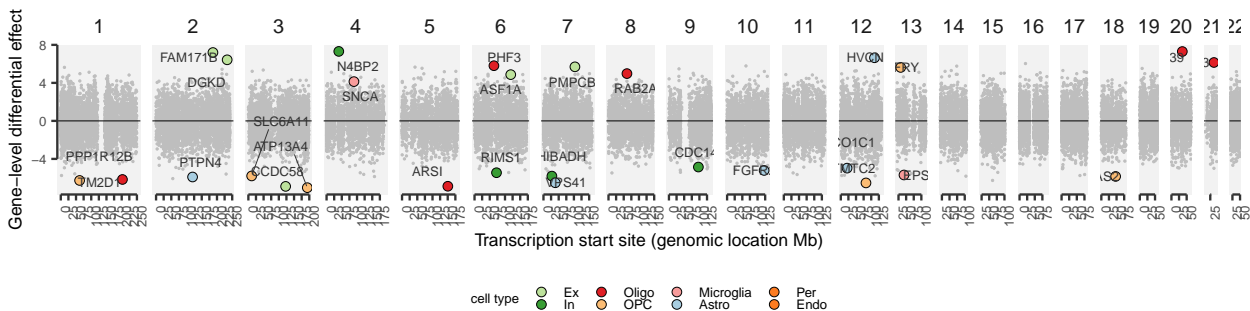

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APOE

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APOE (p = 3.6e−03)

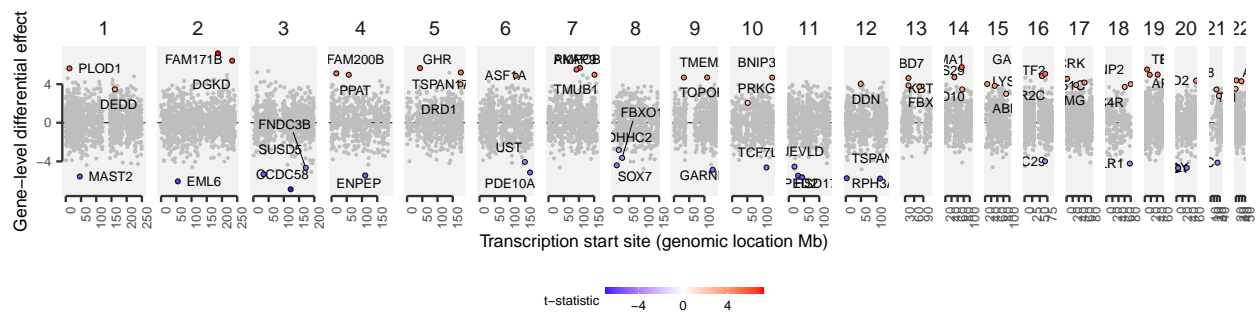
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A genomic view combining all the cell types

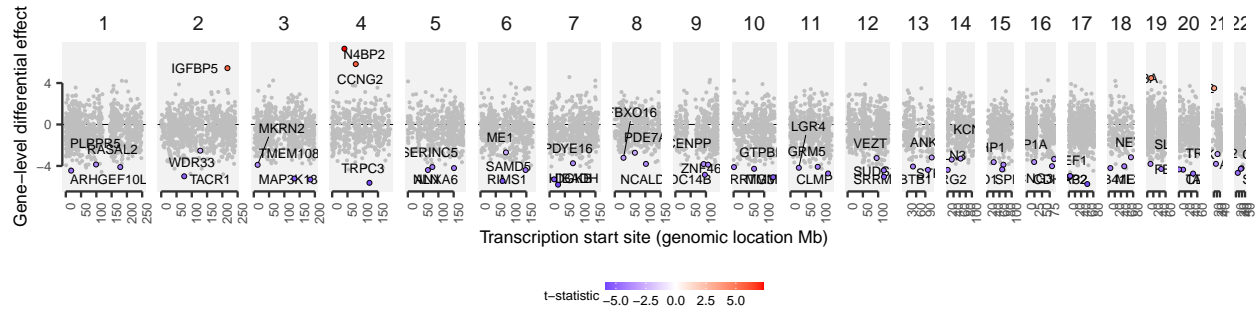Combined genomic view

- PMPCB @ Ex

- ASF1A @ Ex
- CCDC58 @ Ex
- FAM171B @ Ex
- DGKD @ Ex
- CDC14B @ In
- N4BP2 @ In
- HIBADH @ In
- RIMS1 @ In
- TTC3 @ Oligo
- RBM39 @ Oligo
- RAB2A @ Oligo
- PHF3 @ Oligo
- ARSI @ Oligo
- PPP1R12B @ Oligo
- FRY @ OPC
- PIAS2 @ OPC
- SLC6A11 @ OPC
- TMTC2 @ OPC
- TM2D1 @ OPC
- ATP13A4 @ OPC
- EPSTI1 @ Microglia
- SNCA @ Microglia
- VPS41 @ Astro
- SLCO1C1 @ Astro
- FGFR2 @ Astro
- HVCN1 @ Astro
- PTPN4 @ Astro
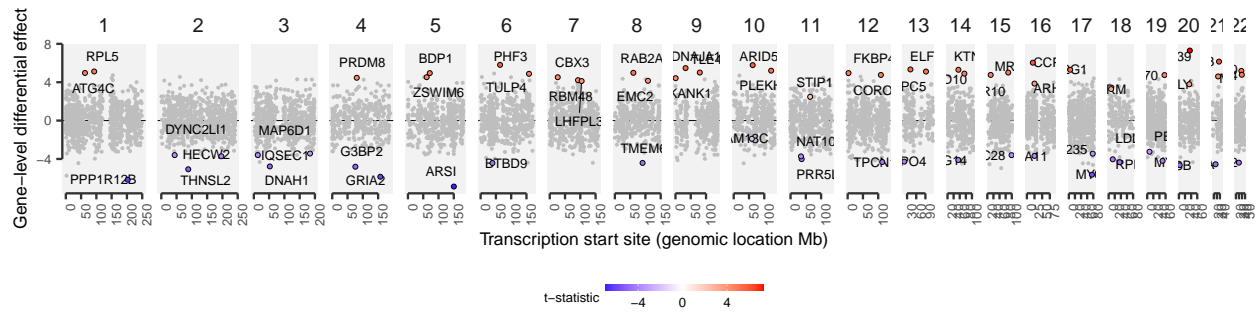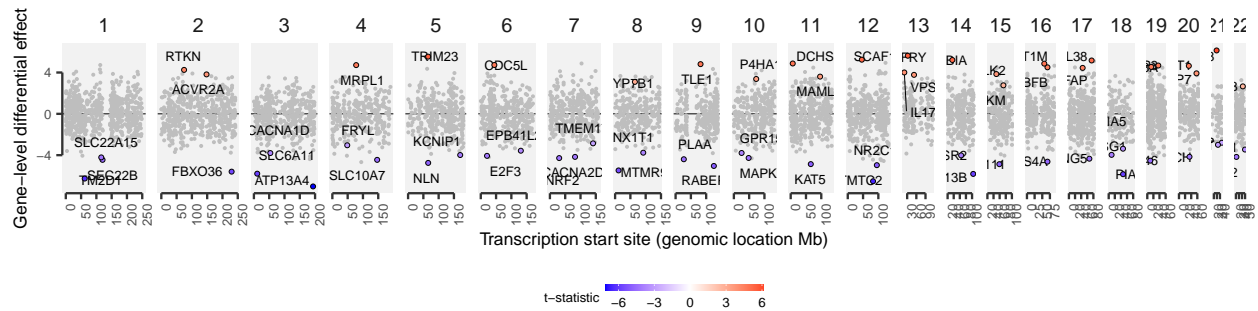
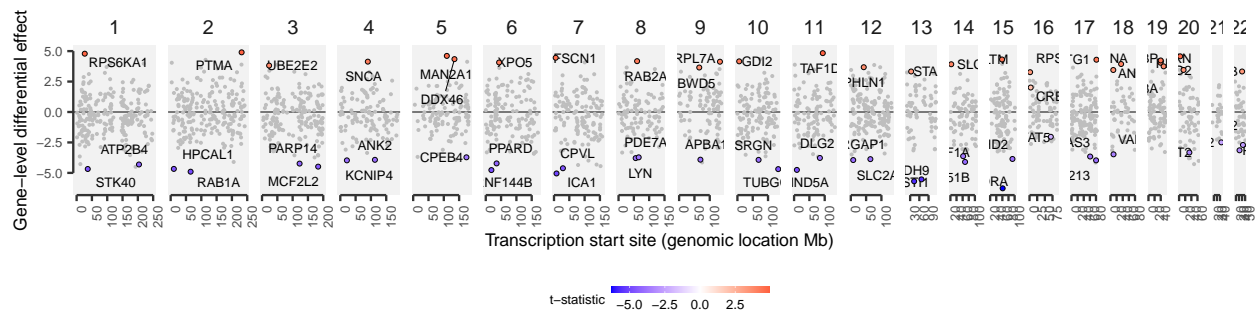## Genomic views for each cell type

Ex

Ex top genes

t−statistic −5.0 −2.5 0.0 2.5 5.0

In

In top genes

t−statistic −4 0 4

Oligo

Oligo top genes

t−statistic −6 −3 0 3 6

OPC

OPC top genes

t−statistic −5.0 −2.5 0.0 2.5

Microglia

Microglia top genes

Astro

Astro top genes

Per

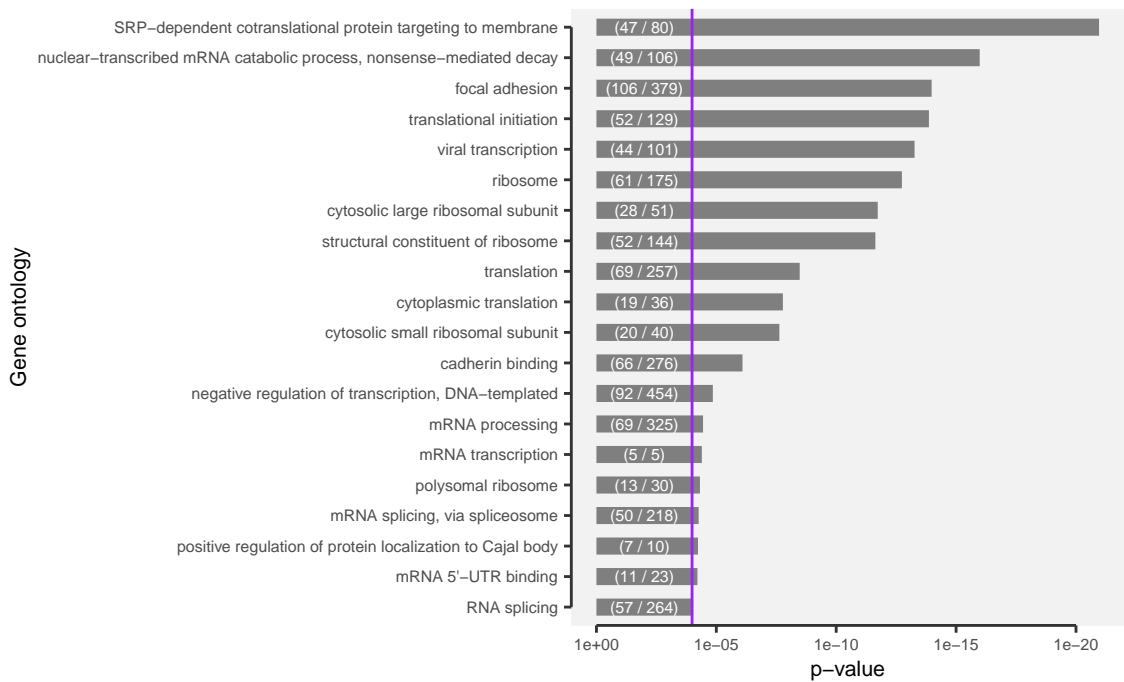Per top genes

Endo

Endo top genes
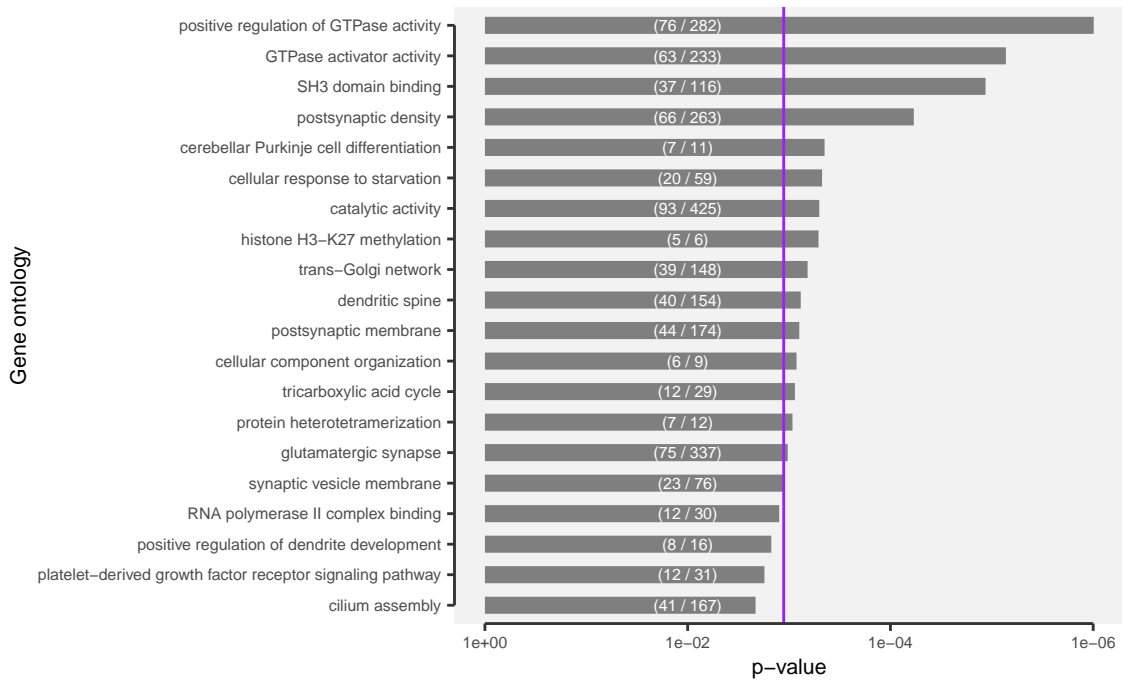
Gene ontology enrichment
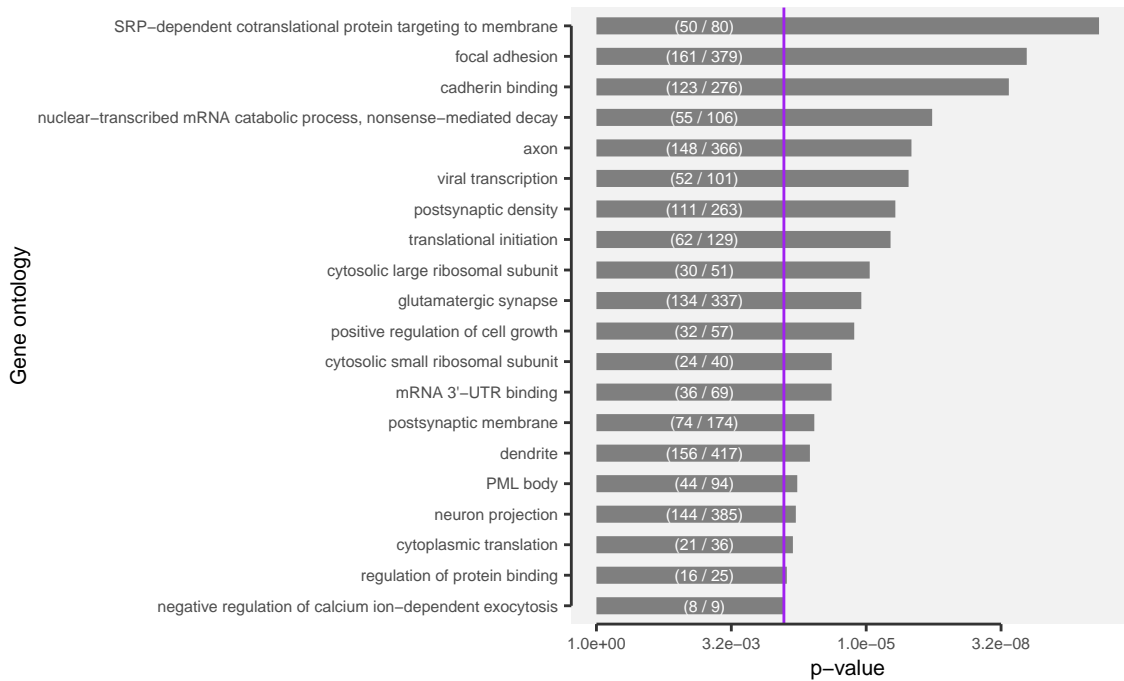
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Up-regulated DEGs (2,092 genes)
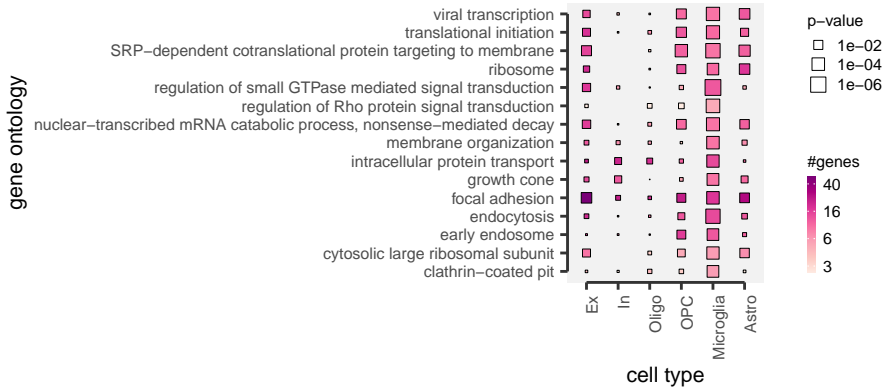

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Down-regulated DEGs (2,317 genes)

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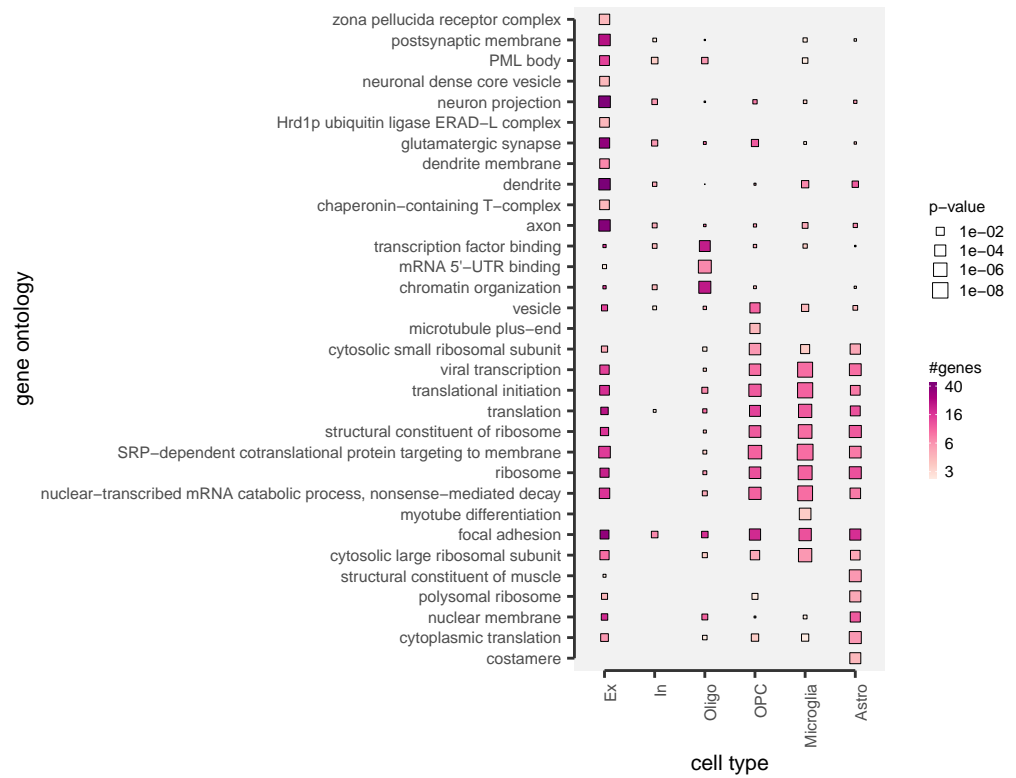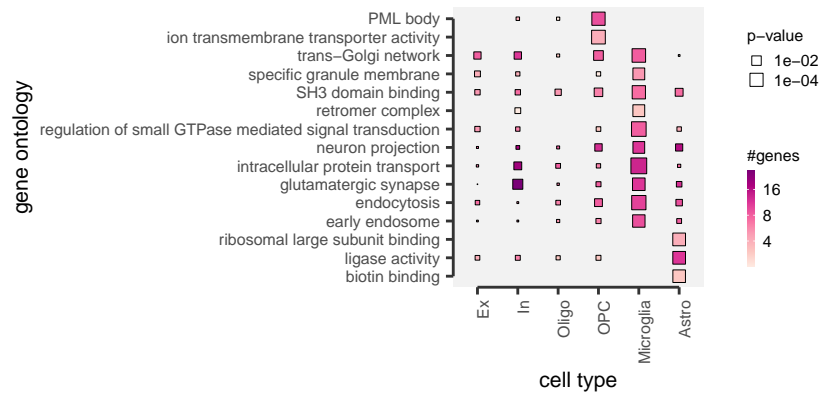## GO enrichment for each cell type

DEGs combined

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DEGs up-regulated

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DEGs down-regulated

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