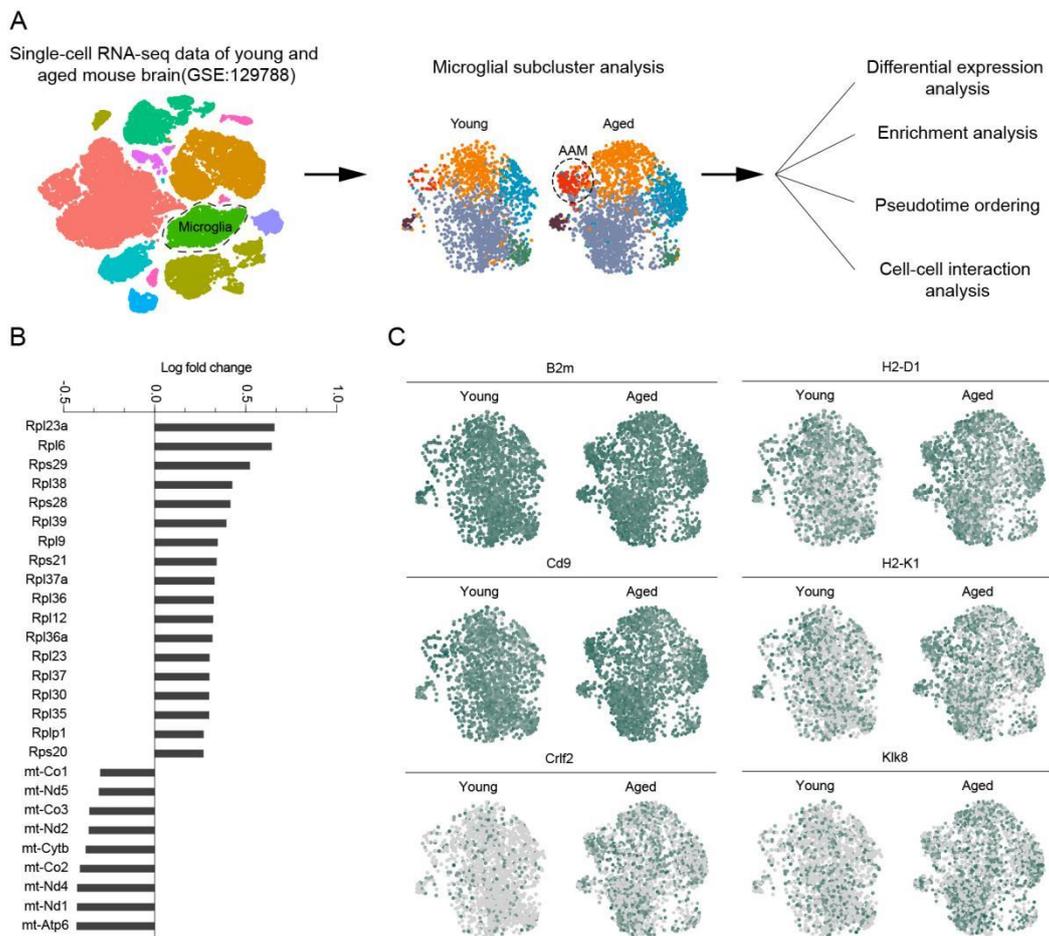


# **A Unique Type of Highly-Activated Microglia Evoking Brain Inflammation via Mif/Cd74 Signaling Axis in Aged Mice**

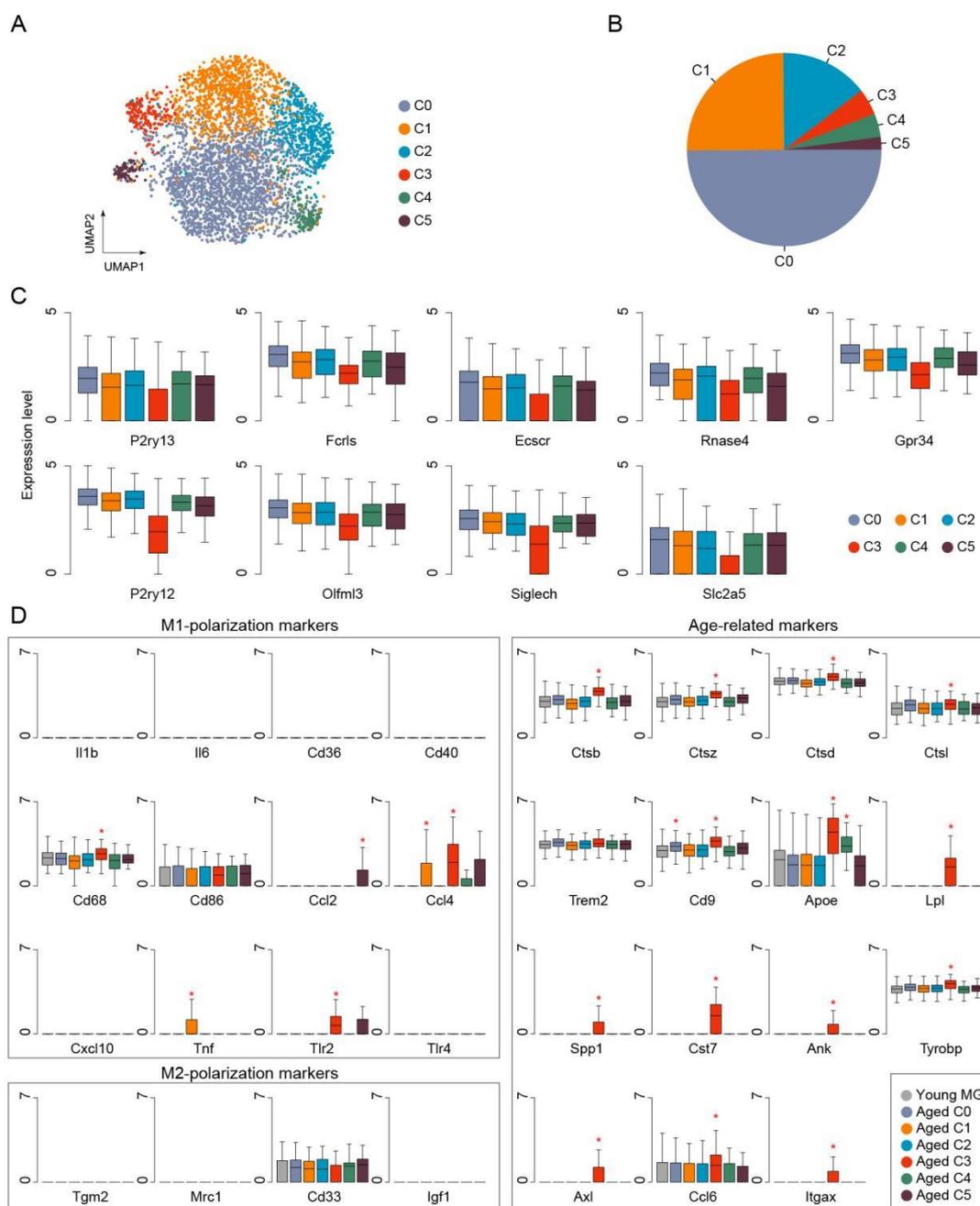
**Chenghao Jin<sup>1,#</sup>, Yijie Shao<sup>1,#</sup>, Xiaotao Zhang<sup>1</sup>, Jiani Xiang<sup>1</sup>, Ruize Zhang<sup>1</sup>, Zeyu Sun<sup>1</sup>, Shuhao Mei<sup>1</sup>, Jingyi Zhou<sup>1,\*</sup>, Jianmin Zhang<sup>1,2,3,\*</sup>, Ligen Shi<sup>1,\*</sup>**

## Supplementary Data



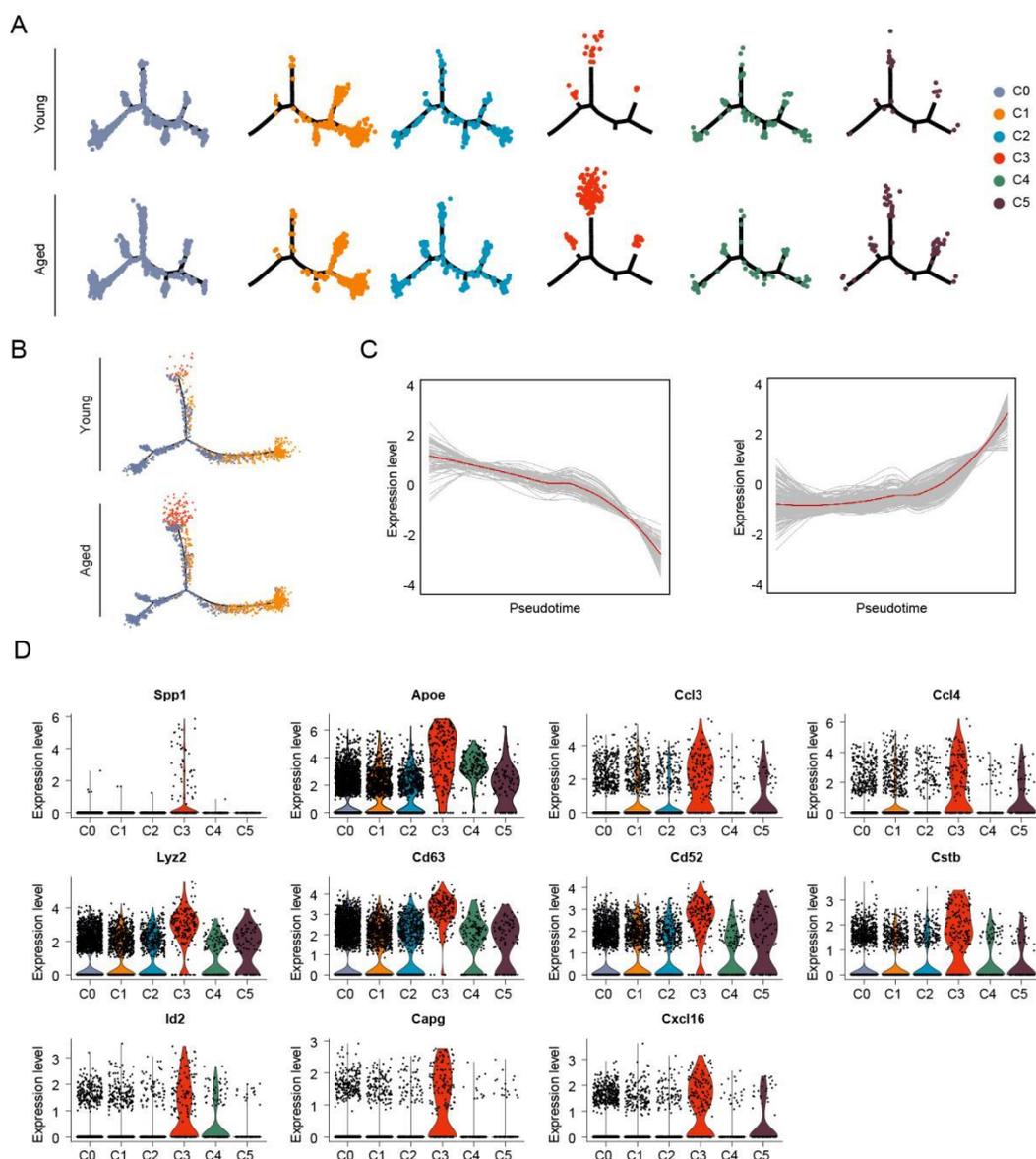
**Supplementary Figure 1. Differences in microglia between young and aged mice.** (A) Workflow of this study. Firstly, the microglia cluster was extracted from scRNA-seq data using clustering analysis based on R package Seurat. Then subcluster analysis on microglia cluster identified a unique group of highly-activated microglia (HAM) in aged mice. Finally, various bioinformatic methods were applied for exploring all aspects of HAM. (B) Bar plot showing the natural log fold change of ribosomal and mitochondrial genes in DEGs of young microglia versus aged microglia. (C) UMAP showing the expression of B2m, Cd9, Crlf2, H2-D1, H2-K1, Klk8 in both young and aged microglia.

## Supplementary Data



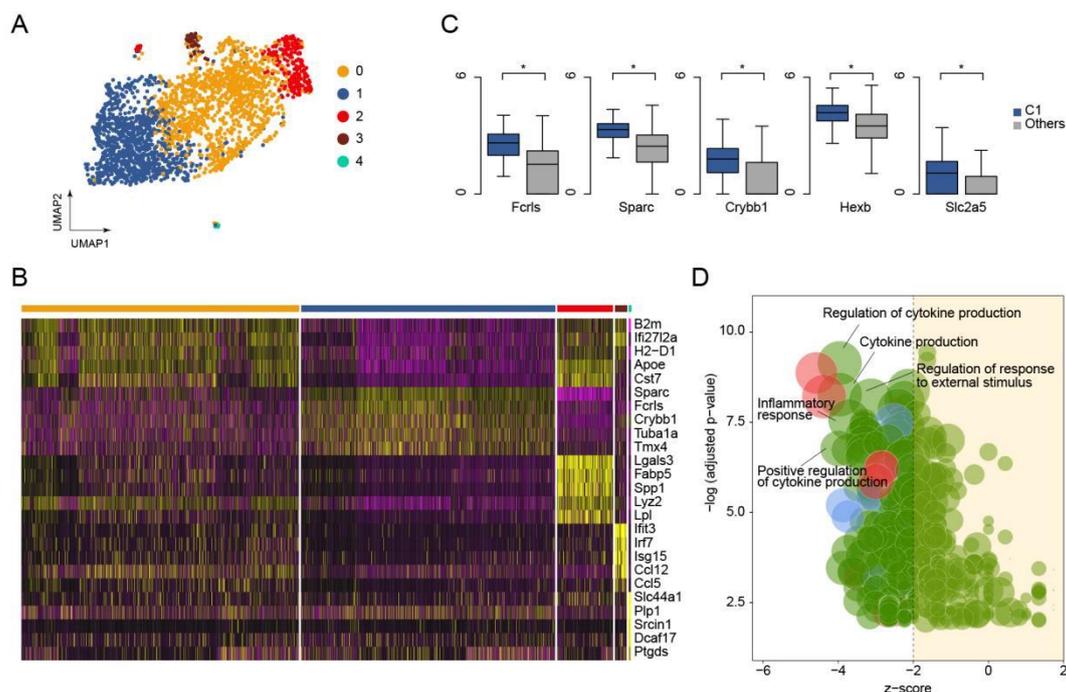
**Supplementary Figure 2. Features of microglial subclusters.** (A) Uniform manifold approximation and projection (UMAP) of all six subcluster(C0-C5) in all microglia. (B) Pie chart showing the proportion of each microglial subcluster in (a). (C) Bar plot showing the differential expression level of nine previously reported marker genes for resting microglia in each microglial subcluster. (D) Bar plot showing the expression level of detected microglial M1-polarization markers, M2-polarization markers and age-related markers in each microglial subcluster. Asterisk indicated the expression level was significantly higher (log fold change > 0.25 and Bonferroni adjusted p-value < 0.05) in the cells of this subcluster than all the other cells.

## Supplementary Data



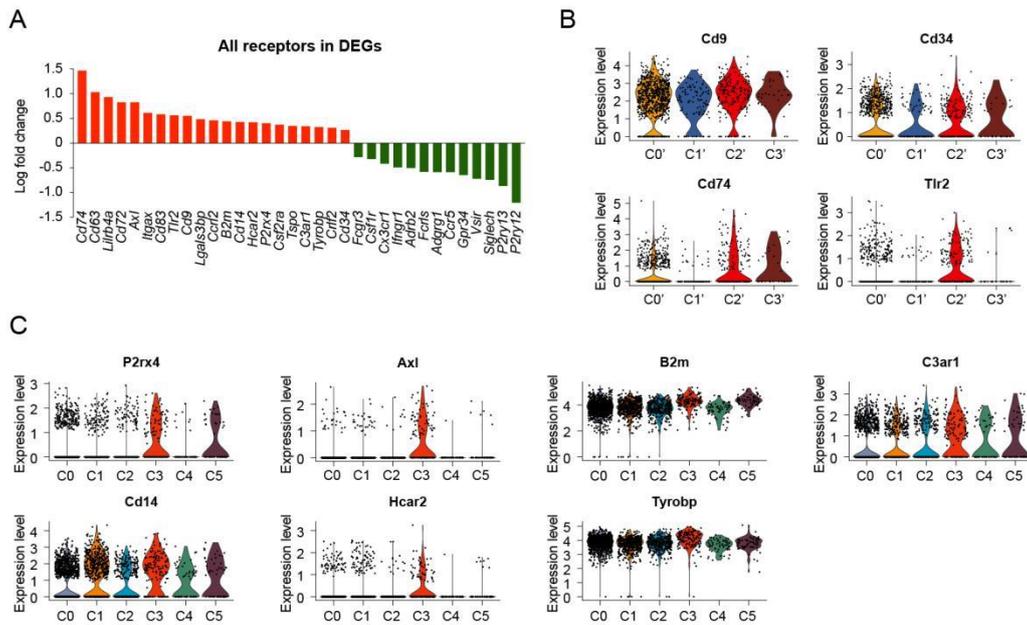
**Supplementary Figure 3. Features of aging-associated microglia.** (A) Cellular pseudotime trajectories of each subclusters both in young and aged microglia generated by DDRTree dimensionality reduction algorithm of Monocle R package. (B) Cellular pseudotime trajectories of subcluster C0, C1 and C3 both in young and aged microglia. (C) Genes in Fig.3d were divided into two groups according to their similarity in variation tendency, plots showing the variation pattern of each group. (D) Violin plot showing the expression level of 11 highly potential marker genes of HAM.

## Supplementary Data



**Supplementary Figure 4. Analysis of scRNA-seq data of microglia in SVZ. (A)** UMAP of all five subcluster(C0-C4) in both young and aged microglia. **(B)** Heatmap visualizing the expression level of top five marker genes in each microglial subclusters. **(C)** Bar plot showing the differential expression level of previously reported marker genes for resting microglia in C1 compared with that in all the other microglial subclusters (\*Bonferroni adjusted P value<0.05). **(D)** Bubble plot showing the enriched GO terms after enrichment analysis using DEGs of microglia in C1 versus all the other microglia.

## Supplementary Data



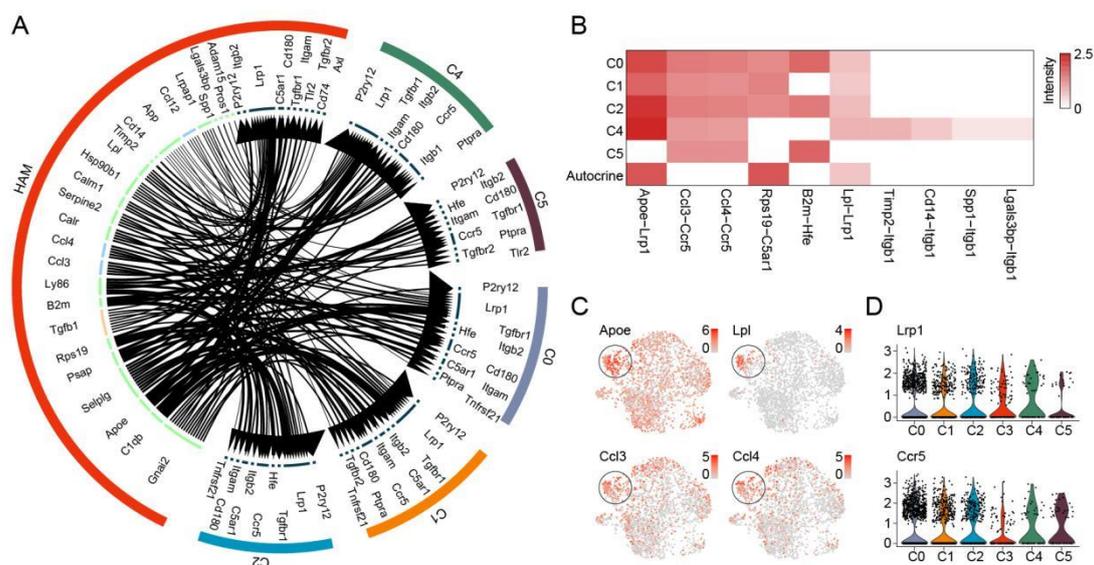
**Supplementary Figure 5. Expression of receptors.** (A) Bar plot showing the fold change of all receptors in DEGs of aged microglia compared with young microglia. (B) Violin plot showing the expression levels of Cd9, Cd34, Cd74, Tlr2 in microglial subclusters of SVZ. (C) Violin plot showing the expression levels of all receptors in microglial subclusters of whole brain.

# Supplementary Data



**Supplementary Figure 6. Gene involvement in GO terms. (A-F)** Heatmap showing the relationship between GO terms associated with cell survival (A), substance and energy metabolism (B), coagulation and hemostasis (C), cytokine secretion (D), chemotaxis (E) and involved genes immunity and inflammation (F).

## Supplementary Data



**Supplementary Figure 7. Interaction between HAM and other microglial subclusters. (A)** Chord plot based on R package iTALK depicting the predicted interaction between HAM and all the other microglial subclusters in aged whole brain. **(B)** Heatmap showing the predicted intensity of interaction of receptor-ligand pairs between HAM and all the other microglial subclusters in aged whole brain. **(C)** UMAP showing the selective expression of four representative ligands of HAM (Apoe, Lpl, Ccl3, Ccl4) in (B). **(D)** Violin plots showing the even expression of two representative receptors of HAM (Lrp1, Ccr5) in (B)

# SUPPLEMENTARY DATA

## Supplementary Tables

**Supplementary Table 1.** Differentially expressed genes in microglia from aged mice versus young mice.

| Genes   | P-value  | Average logFC | Percentage in aged | Percentage in young | Adjusted P-value |
|---------|----------|---------------|--------------------|---------------------|------------------|
| Crlf2   | 8.22E-86 | 0.695793543   | 0.476              | 0.165               | 1.05E-81         |
| Rpl23a  | 6.56E-66 | 0.658431445   | 0.43               | 0.176               | 8.42E-62         |
| Rpl6    | 4.04E-83 | 0.6426102     | 0.711              | 0.419               | 5.19E-79         |
| Lyz2    | 1.69E-58 | 0.597357896   | 0.712              | 0.49                | 2.16E-54         |
| Rps29   | 9.31E-64 | 0.52379043    | 0.964              | 0.911               | 1.19E-59         |
| Ppfla4  | 6.62E-71 | 0.513711859   | 0.55               | 0.238               | 8.49E-67         |
| Ccl4    | 2.28E-15 | 0.446561388   | 0.265              | 0.156               | 2.92E-11         |
| Ccl3    | 1.00E-23 | 0.430851659   | 0.332              | 0.185               | 1.28E-19         |
| Rpl38   | 1.41E-41 | 0.425835654   | 0.815              | 0.66                | 1.80E-37         |
| Cd52    | 8.61E-30 | 0.419667466   | 0.617              | 0.439               | 1.10E-25         |
| Rps28   | 8.92E-29 | 0.415904396   | 0.664              | 0.501               | 1.14E-24         |
| Apoe    | 1.48E-06 | 0.412138576   | 0.704              | 0.749               | 0.018973119      |
| Rpl39   | 7.50E-66 | 0.393824187   | 0.96               | 0.865               | 9.62E-62         |
| Lsp1    | 4.64E-28 | 0.391642635   | 0.3                | 0.146               | 5.95E-24         |
| Klk8    | 9.32E-35 | 0.366723018   | 0.512              | 0.304               | 1.20E-30         |
| Cd63    | 3.50E-33 | 0.363524713   | 0.797              | 0.662               | 4.49E-29         |
| H2-D1   | 8.17E-32 | 0.356693999   | 0.799              | 0.662               | 1.05E-27         |
| Rpl9    | 1.23E-23 | 0.346848615   | 0.381              | 0.228               | 1.57E-19         |
| Rps21   | 3.33E-41 | 0.339882732   | 0.866              | 0.714               | 4.27E-37         |
| Rpl37a  | 7.43E-50 | 0.32842553    | 0.973              | 0.914               | 9.53E-46         |
| Rpl36   | 8.74E-32 | 0.32488124    | 0.848              | 0.73                | 1.12E-27         |
| Rpl12   | 8.34E-36 | 0.320968576   | 0.813              | 0.688               | 1.07E-31         |
| Rpl36a  | 1.16E-34 | 0.31709392    | 0.854              | 0.725               | 1.49E-30         |
| Tpt1    | 1.92E-42 | 0.304401634   | 0.927              | 0.851               | 2.46E-38         |
| H2-K1   | 1.78E-24 | 0.304005424   | 0.61               | 0.436               | 2.28E-20         |
| Rpl23   | 3.77E-45 | 0.301519819   | 0.95               | 0.896               | 4.83E-41         |
| Rpl37   | 7.81E-35 | 0.300871489   | 0.96               | 0.889               | 1.00E-30         |
| Rpl30   | 2.16E-44 | 0.299372655   | 0.914              | 0.81                | 2.77E-40         |
| Rpl35   | 3.21E-20 | 0.299063477   | 0.652              | 0.5                 | 4.12E-16         |
| Upk1b   | 6.75E-23 | 0.288091121   | 0.319              | 0.169               | 8.66E-19         |
| Rplp1   | 5.66E-50 | 0.268854684   | 0.98               | 0.934               | 7.26E-46         |
| Rps20   | 3.17E-34 | 0.268213256   | 0.903              | 0.807               | 4.07E-30         |
| Actb    | 5.51E-25 | 0.260931102   | 0.992              | 0.982               | 7.07E-21         |
| B2m     | 1.41E-42 | 0.258407813   | 0.995              | 0.994               | 1.81E-38         |
| Cd9     | 9.09E-31 | 0.250669479   | 0.962              | 0.939               | 1.17E-26         |
| Fcrls   | 6.01E-26 | -0.254372786  | 0.899              | 0.939               | 7.71E-22         |
| Pld1    | 1.65E-10 | -0.268801177  | 0.233              | 0.308               | 2.11E-06         |
| mt-Co1  | 3.85E-47 | -0.29908548   | 0.999              | 0.998               | 4.93E-43         |
| mt-Nd5  | 2.22E-13 | -0.306373545  | 0.434              | 0.51                | 2.84E-09         |
| P2ry12  | 4.53E-64 | -0.312783131  | 0.968              | 0.99                | 5.81E-60         |
| Mt3     | 2.11E-09 | -0.319009042  | 0.239              | 0.31                | 2.71E-05         |
| Serinc3 | 1.87E-22 | -0.323520542  | 0.736              | 0.788               | 2.40E-18         |
| Csflr   | 1.24E-89 | -0.347559437  | 0.954              | 0.988               | 1.60E-85         |
| Rsrp1   | 6.33E-33 | -0.354383071  | 0.713              | 0.78                | 8.11E-29         |
| Ndrp2   | 3.12E-13 | -0.354546998  | 0.205              | 0.291               | 4.00E-09         |
| mt-Co3  | 1.56E-79 | -0.358505313  | 1                  | 0.999               | 2.01E-75         |
| mt-Nd2  | 5.25E-39 | -0.36215292   | 0.878              | 0.921               | 6.73E-35         |

## SUPPLEMENTARY DATA

|         |           |              |       |       |           |
|---------|-----------|--------------|-------|-------|-----------|
| Sepw1   | 3.30E-16  | -0.374408474 | 0.369 | 0.45  | 4.23E-12  |
| mt-Cytb | 6.73E-82  | -0.378390457 | 0.997 | 0.999 | 8.64E-78  |
| Cpe     | 8.80E-14  | -0.397851753 | 0.234 | 0.321 | 1.13E-09  |
| mt-Co2  | 8.50E-76  | -0.410546435 | 0.988 | 0.988 | 1.09E-71  |
| Pcsk1n  | 7.47E-20  | -0.410632381 | 0.227 | 0.337 | 9.59E-16  |
| Aldoc   | 3.84E-17  | -0.410915633 | 0.241 | 0.342 | 4.92E-13  |
| mt-Nd4  | 2.03E-87  | -0.425814425 | 0.986 | 0.995 | 2.61E-83  |
| mt-Nd1  | 6.21E-109 | -0.426912291 | 0.996 | 0.998 | 7.96E-105 |
| mt-Atp6 | 2.36E-108 | -0.42883186  | 1     | 0.999 | 3.03E-104 |

**Supplementary Table 2.** Functional enrichment results of DEGs for six subclusters of microglia.

| C0vsOthers   |         |
|--|---------|
| Terms  | Z-score |
| transcription factor AP-1 complex  | -2      |
| response to cAMP   | -2      |
| cellular response to calcium ion   | -2      |
| response to organophosphorus   | -2      |
| response to purine-containing compound   | -2      |
| response to calcium ion  | -2      |
| cellular response to metal ion   | -2      |
| RNA polymerase II transcription factor complex   | -2      |
| nuclear transcription factor complex   | -2      |
| cellular response to inorganic substance   | -2      |
| transcription coactivator activity   | -2      |
| response to metal ion  | -2      |
| DNA-binding transcription repressor activity, RNA polymerase II-specific                         | -2      |
| positive regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay | -2      |
| regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay          | -2      |
| p38MAPK cascade  | -2      |
| nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay                        | -2      |
| positive regulation of mRNA catabolic process  | -2      |
| nuclear-transcribed mRNA catabolic process   | -2      |
| regulation of mRNA catabolic process   | -2      |
| erythrocyte differentiation  | -2      |
| erythrocyte homeostasis  | -2      |
| negative regulation of cellular amide metabolic process  | -2      |
| myeloid cell homeostasis   | -2      |
| cytoplasmic ribonucleoprotein granule  | -2      |
| mRNA catabolic process   | -2      |
| ribonucleoprotein granule  | -2      |
| RNA catabolic process  | -2      |
| negative regulation of cellular catabolic process  | -2      |
| stress-activated MAPK cascade  | -2      |
| negative regulation of catabolic process   | -2      |
| stress-activated protein kinase signaling cascade  | -2      |
| RNA polymerase II activating transcription factor binding  | -2      |
| positive regulation of myeloid leukocyte differentiation   | -2      |
| SMAD binding   | -2      |
| activating transcription factor binding  | -2      |
| positive regulation of myeloid cell differentiation  | -2      |
| regulation of myeloid leukocyte differentiation  | -2      |

## SUPPLEMENTARY DATA

|  |              |
|--|--------------|
| transforming growth factor beta receptor signaling pathway                                   | -2           |
| RNA polymerase II transcription factor binding   | -2           |
| camera-type eye development  | -2           |
| vascular process in circulatory system   | -2           |
| positive regulation of ion transport   | -2           |
| regulation of small molecule metabolic process   | -2           |
| negative regulation of protein kinase activity   | -2           |
| negative regulation of kinase activity   | -2           |
| modification by host of symbiont morphology or physiology                                    | -2           |
| positive regulation of viral process   | -2           |
| modification of morphology or physiology of other organism involved in symbiotic interaction | -2           |
| modification of morphology or physiology of other organism                                   | -2           |
| positive regulation of ERK1 and ERK2 cascade   | -2           |
| positive regulation of neuron apoptotic process  | -2           |
| learning or memory   | -2           |
| cognition  | -2           |
| positive regulation of tumor necrosis factor production                                      | -2           |
| positive regulation of tumor necrosis factor superfamily cytokine production                 | -2           |
| leukocyte migration  | -2           |
| cellular response to hypoxia   | -2           |
| cellular response to decreased oxygen levels   | -2           |
| cellular response to oxygen levels   | -2           |
| response to hypoxia  | -2           |
| response to decreased oxygen levels  | -2           |
| T cell differentiation   | -2           |
| response to oxygen levels  | -2           |
| apoptotic mitochondrial changes  | -2           |
| regulation of extrinsic apoptotic signaling pathway  | -2           |
| extrinsic apoptotic signaling pathway  | -2           |
| cellular response to oxidative stress  | -2           |
| intrinsic apoptotic signaling pathway  | -2           |
| embryonic placenta development   | -2           |
| placenta development   | -2           |
| cytokine biosynthetic process  | -2           |
| cytokine metabolic process   | -2           |
| muscle cell proliferation  | -2           |
| response to toxic substance  | -2           |
| myelin sheath  | -2           |
| negative regulation of catalytic activity  | -2.121320344 |
| blood vessel morphogenesis   | -2.121320344 |
| response to mechanical stimulus  | -2.236067977 |
| nuclear chromatin  | -2.236067977 |
| response to inorganic substance  | -2.236067977 |
| skeletal muscle cell differentiation   | -2.236067977 |
| positive regulation of mRNA metabolic process  | -2.236067977 |
| cellular response to tumor necrosis factor   | -2.236067977 |
| regulation of mRNA metabolic process   | -2.236067977 |
| regulation of translation  | -2.236067977 |
| nucleobase-containing compound catabolic process   | -2.236067977 |
| aromatic compound catabolic process  | -2.236067977 |
| posttranscriptional regulation of gene expression  | -2.236067977 |
| positive regulation of leukocyte differentiation   | -2.236067977 |

# SUPPLEMENTARY DATA

|   |              |
|---|--------------|
| cellular response to transforming growth factor beta stimulus                     | -2.236067977 |
| positive regulation of hemopoiesis  | -2.236067977 |
| response to transforming growth factor beta                                       | -2.236067977 |
| regulation of leukocyte differentiation   | -2.236067977 |
| transmembrane receptor protein serine/threonine kinase signaling pathway          | -2.236067977 |
| protein heterodimerization activity   | -2.236067977 |
| negative regulation of inflammatory response                                      | -2.236067977 |
| negative regulation of defense response   | -2.236067977 |
| regulation of anatomical structure size   | -2.236067977 |
| negative regulation of transferase activity                                       | -2.236067977 |
| interaction with symbiont   | -2.236067977 |
| positive regulation of multi-organism process                                     | -2.236067977 |
| positive regulation of MAPK cascade   | -2.236067977 |
| positive regulation of neuron death   | -2.236067977 |
| regulation of epithelial cell proliferation                                       | -2.236067977 |
| epithelial cell proliferation   | -2.236067977 |
| response to wounding  | -2.236067977 |
| regulation of tumor necrosis factor production                                    | -2.236067977 |
| regulation of tumor necrosis factor superfamily cytokine production               | -2.236067977 |
| tumor necrosis factor production  | -2.236067977 |
| tumor necrosis factor superfamily cytokine production                             | -2.236067977 |
| cytokine-mediated signaling pathway   | -2.236067977 |
| response to oxidative stress  | -2.236067977 |
| regulation of apoptotic signaling pathway   | -2.236067977 |
| axon development  | -2.236067977 |
| regulation of cellular catabolic process  | -2.333333333 |
| positive regulation of apoptotic process  | -2.333333333 |
| positive regulation of programmed cell death                                      | -2.333333333 |
| response to radiation   | -2.449489743 |
| transcription coregulator activity  | -2.449489743 |
| cellular response to hormone stimulus   | -2.449489743 |
| regulation of transcription from RNA polymerase II promoter in response to stress | -2.449489743 |
| regulation of DNA-templated transcription in response to stress                   | -2.449489743 |
| response to tumor necrosis factor   | -2.449489743 |
| homeostasis of number of cells  | -2.449489743 |
| regulation of cellular amide metabolic process                                    | -2.449489743 |
| cellular nitrogen compound catabolic process                                      | -2.449489743 |
| negative regulation of immune system process                                      | -2.449489743 |
| heterocycle catabolic process   | -2.449489743 |
| negative regulation of cell differentiation                                       | -2.449489743 |
| regulation of myeloid cell differentiation  | -2.449489743 |
| myeloid leukocyte differentiation   | -2.449489743 |
| negative regulation of response to external stimulus                              | -2.449489743 |
| negative regulation of intracellular signal transduction                          | -2.449489743 |
| regulation of viral process   | -2.449489743 |
| regulation of symbiosis, encompassing mutualism through parasitism                | -2.449489743 |
| viral process   | -2.449489743 |
| regulation of ERK1 and ERK2 cascade   | -2.449489743 |
| regulation of neuron apoptotic process  | -2.449489743 |
| epithelial cell differentiation   | -2.449489743 |
| developmental growth  | -2.449489743 |
| positive regulation of cytokine production  | -2.449489743 |

## SUPPLEMENTARY DATA

|   |              |
|---|--------------|
| cellular response to hypoxia  | -2.449489743 |
| apoptotic signaling pathway   | -2.449489743 |
| protein domain specific binding   | -2.449489743 |
| in utero embryonic development  | -2.449489743 |
| cytokine biosynthetic process   | -2.449489743 |
| positive regulation of cell death   | -2.529822128 |
| blood vessel development  | -2.529822128 |
| vasculature development   | -2.529822128 |
| cardiovascular system development   | -2.529822128 |
| response to organic cyclic compound   | -2.529822128 |
| response to lipopolysaccharide  | -2.645751311 |
| response to molecule of bacterial origin  | -2.645751311 |
| DNA-binding transcription activator activity, RNA polymerase II-specific          | -2.645751311 |
| response to hormone   | -2.645751311 |
| regulation of transcription from RNA polymerase II promoter in response to stress | -2.645751311 |
| organic cyclic compound catabolic process   | -2.645751311 |
| regulation of hemopoiesis   | -2.645751311 |
| cellular response to growth factor stimulus                                       | -2.645751311 |
| regulation of inflammatory response   | -2.645751311 |
| ERK1 and ERK2 cascade   | -2.645751311 |
| symbiont process  | -2.645751311 |
| regulation of multi-organism process  | -2.645751311 |
| interspecies interaction between organisms  | -2.645751311 |
| regulation of MAPK cascade  | -2.645751311 |
| neuron apoptotic process  | -2.645751311 |
| regulation of neuron death  | -2.645751311 |
| myelin sheath   | -2.645751311 |
| RNA polymerase II proximal promoter sequence-specific DNA binding                 | -2.828427125 |
| proximal promoter sequence-specific DNA binding                                   | -2.828427125 |
| skeletal muscle tissue development  | -2.828427125 |
| skeletal muscle organ development   | -2.828427125 |
| muscle organ development  | -2.828427125 |
| striated muscle tissue development  | -2.828427125 |
| muscle tissue development   | -2.828427125 |
| peptide metabolic process   | -2.828427125 |
| response to growth factor   | -2.828427125 |
| regulation of defense response  | -2.828427125 |
| negative regulation of protein phosphorylation                                    | -2.828427125 |
| negative regulation of protein modification process                               | -2.828427125 |
| neuron death  | -2.828427125 |
| regulation of cytokine production   | -2.828427125 |
| regulation of cellular response to stress   | -2.828427125 |
| embryonic placenta development  | -2.828427125 |
| myeloid cell differentiation  | -3           |
| leukocyte differentiation   | -3           |
| regulation of response to external stimulus                                       | -3           |
| negative regulation of phosphorylation  | -3           |
| negative regulation of phosphorus metabolic process                               | -3           |
| negative regulation of phosphate metabolic process                                | -3           |
| MAPK cascade  | -3           |
| cytokine production   | -3           |
| negative regulation of phosphorylation  | -3.050851079 |

## SUPPLEMENTARY DATA

|  |              |
|--|--------------|
| positive regulation of cell death  | -3.050851079 |
| blood vessel development   | -3.050851079 |
| inflammatory response  | -3.152963125 |
| skeletal muscle tissue development   | -3.16227766  |
| muscle structure development   | -3.16227766  |
| regulation of tumor necrosis factor production   | -3.207134903 |
| transcription factor binding   | -3.31662479  |
| inflammatory response  | -3.31662479  |
| DNA-binding transcription factor activity, RNA polymerase II-specific                            | -3.464101615 |
| interaction with symbiont  | -3.605551275 |
| apoptotic mitochondrial changes  | -3.741657387 |
| myeloid cell differentiation   | -4.242640687 |
| positive regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay | -4.706787243 |
| transcription factor AP-1 complex  | -4.898979486 |
| C1vsC0   |              |
| Terms  | Z-score      |
| DNA-binding transcription factor activity, RNA polymerase II-specific                            | 3.605551275  |
| transcription factor binding   | 3.16227766   |
| myeloid cell differentiation   | 3.16227766   |
| leukocyte differentiation  | 3.16227766   |
| inflammatory response  | 3.16227766   |
| RNA polymerase II proximal promoter sequence-specific DNA binding                                | 3            |
| regulation of response to external stimulus  | 3            |
| proximal promoter sequence-specific DNA binding  | 3            |
| muscle structure development   | 3            |
| cytokine production  | 3            |
| striated muscle tissue development   | 2.828427125  |
| skeletal muscle tissue development   | 2.828427125  |
| skeletal muscle organ development  | 2.828427125  |
| regulation of transcription from RNA polymerase II promoter in response to stress                | 2.828427125  |
| regulation of hemopoiesis  | 2.828427125  |
| regulation of DNA-templated transcription in response to stress                                  | 2.828427125  |
| regulation of defense response   | 2.828427125  |
| regulation of cytokine production  | 2.828427125  |
| regulation of cellular response to stress  | 2.828427125  |
| peptide metabolic process  | 2.828427125  |
| neuron death   | 2.828427125  |
| muscle tissue development  | 2.828427125  |
| muscle organ development   | 2.828427125  |
| MAPK cascade   | 2.828427125  |
| DNA-binding transcription activator activity, RNA polymerase II-specific                         | 2.828427125  |
| apoptotic signaling pathway  | 2.828427125  |
| positive regulation of cell death  | 2.713602101  |
| response to molecule of bacterial origin   | 2.645751311  |
| response to lipopolysaccharide   | 2.645751311  |
| response to hormone  | 2.645751311  |
| regulation of neuron death   | 2.645751311  |
| regulation of myeloid cell differentiation   | 2.645751311  |
| regulation of inflammatory response  | 2.645751311  |
| protein domain specific binding  | 2.645751311  |
| neuron apoptotic process   | 2.645751311  |
| negative regulation of phosphorylation   | 2.645751311  |

# SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| negative regulation of phosphorus metabolic process                      | 2.645751311 |
| negative regulation of phosphate metabolic process                       | 2.645751311 |
| negative regulation of immune system process                             | 2.645751311 |
| myeloid leukocyte differentiation  | 2.645751311 |
| in utero embryonic development   | 2.645751311 |
| chromatin binding  | 2.645751311 |
| response to growth factor  | 2.529822128 |
| transmembrane receptor protein serine/threonine kinase signaling pathway | 2.449489743 |
| translation  | 2.449489743 |
| transcription coregulator activity                                       | 2.449489743 |
| T cell activation  | 2.449489743 |
| symbiont process   | 2.449489743 |
| response to tumor necrosis factor  | 2.449489743 |
| regulation of neuron apoptotic process                                   | 2.449489743 |
| regulation of leukocyte differentiation                                  | 2.449489743 |
| regulation of apoptotic signaling pathway                                | 2.449489743 |
| protein heterodimerization activity                                      | 2.449489743 |
| positive regulation of cytokine production                               | 2.449489743 |
| peptide biosynthetic process   | 2.449489743 |
| nuclear chromosome part  | 2.449489743 |
| nuclear chromosome   | 2.449489743 |
| nuclear chromatin  | 2.449489743 |
| negative regulation of protein phosphorylation                           | 2.449489743 |
| negative regulation of protein modification process                      | 2.449489743 |
| negative regulation of intracellular signal transduction                 | 2.449489743 |
| negative regulation of cell proliferation                                | 2.449489743 |
| intrinsic apoptotic signaling pathway                                    | 2.449489743 |
| interspecies interaction between organisms                               | 2.449489743 |
| homeostasis of number of cells   | 2.449489743 |
| ERK1 and ERK2 cascade  | 2.449489743 |
| chromatin  | 2.449489743 |
| cellular response to hormone stimulus                                    | 2.449489743 |
| vasculature development  | 2.333333333 |
| response to organic cyclic compound                                      | 2.333333333 |
| positive regulation of programmed cell death                             | 2.333333333 |
| positive regulation of apoptotic process                                 | 2.333333333 |
| cellular response to growth factor stimulus                              | 2.333333333 |
| cardiovascular system development  | 2.333333333 |
| blood vessel development   | 2.333333333 |
| viral process  | 2.236067977 |
| ubiquitin-like protein ligase binding                                    | 2.236067977 |
| transcription factor complex   | 2.236067977 |
| SMAD binding   | 2.236067977 |
| skeletal muscle cell differentiation                                     | 2.236067977 |
| RNA polymerase II transcription factor complex                           | 2.236067977 |
| response to wounding   | 2.236067977 |
| response to transforming growth factor beta                              | 2.236067977 |
| response to radiation  | 2.236067977 |
| response to mechanical stimulus  | 2.236067977 |
| response to inorganic substance  | 2.236067977 |
| reproductive system development  | 2.236067977 |
| reproductive structure development                                       | 2.236067977 |

# SUPPLEMENTARY DATA

|   |             |
|---|-------------|
| regulation of viral process   | 2.236067977 |
| regulation of symbiosis, encompassing mutualism through parasitism                      | 2.236067977 |
| regulation of myeloid leukocyte differentiation   | 2.236067977 |
| regulation of multi-organism process  | 2.236067977 |
| regulation of mRNA metabolic process  | 2.236067977 |
| regulation of ERK1 and ERK2 cascade   | 2.236067977 |
| positive regulation of neuron death   | 2.236067977 |
| positive regulation of mRNA metabolic process   | 2.236067977 |
| positive regulation of leukocyte differentiation  | 2.236067977 |
| positive regulation of hemopoiesis  | 2.236067977 |
| placenta development  | 2.236067977 |
| organic cyclic compound catabolic process   | 2.236067977 |
| nucleobase-containing compound catabolic process  | 2.236067977 |
| nuclear transcription factor complex  | 2.236067977 |
| negative regulation of response to external stimulus                                    | 2.236067977 |
| heterocycle catabolic process   | 2.236067977 |
| extrinsic apoptotic signaling pathway   | 2.236067977 |
| epithelial cell proliferation   | 2.236067977 |
| embryonic placenta development  | 2.236067977 |
| embryonic organ development   | 2.236067977 |
| DNA-binding transcription repressor activity, RNA polymerase II-specific                | 2.236067977 |
| cytokine-mediated signaling pathway   | 2.236067977 |
| cellular response to tumor necrosis factor  | 2.236067977 |
| cellular response to transforming growth factor beta stimulus                           | 2.236067977 |
| cellular nitrogen compound catabolic process  | 2.236067977 |
| aromatic compound catabolic process   | 2.236067977 |
| regulation of cellular catabolic process  | 2.121320344 |
| epithelial cell differentiation   | 2.121320344 |
| ubiquitin protein ligase binding  | 2           |
| tumor necrosis factor superfamily cytokine production                                   | 2           |
| tumor necrosis factor production  | 2           |
| transforming growth factor beta receptor signaling pathway                              | 2           |
| transcription factor AP-1 complex   | 2           |
| transcription coactivator activity  | 2           |
| temperature homeostasis   | 2           |
| T cell differentiation  | 2           |
| stress-activated protein kinase signaling cascade                                       | 2           |
| stress-activated MAPK cascade   | 2           |
| RNA catabolic process   | 2           |
| response to purine-containing compound  | 2           |
| response to organophosphorus  | 2           |
| response to metal ion   | 2           |
| response to interleukin-1   | 2           |
| response to endoplasmic reticulum stress  | 2           |
| response to cAMP  | 2           |
| response to calcium ion   | 2           |
| regulation of tumor necrosis factor superfamily cytokine production                     | 2           |
| regulation of tumor necrosis factor production  | 2           |
| regulation of translation   | 2           |
| regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay | 2           |
| regulation of mRNA catabolic process  | 2           |
| regulation of intrinsic apoptotic signaling pathway                                     | 2           |

# SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| regulation of extrinsic apoptotic signaling pathway  | 2           |
| reactive oxygen species metabolic process  | 2           |
| positive regulation of response to external stimulus   | 2           |
| positive regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay | 2           |
| positive regulation of neuron apoptotic process  | 2           |
| positive regulation of myeloid leukocyte differentiation   | 2           |
| positive regulation of myeloid cell differentiation  | 2           |
| positive regulation of mRNA catabolic process  | 2           |
| p38MAPK cascade  | 2           |
| osteoclast differentiation   | 2           |
| nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay                        | 2           |
| nuclear-transcribed mRNA catabolic process   | 2           |
| negative regulation of transcription from RNA polymerase II promoter in response to stress       | 2           |
| negative regulation of inflammatory response   | 2           |
| negative regulation of defense response  | 2           |
| negative regulation of cellular catabolic process  | 2           |
| negative regulation of catabolic process   | 2           |
| negative regulation of apoptotic signaling pathway   | 2           |
| myeloid cell homeostasis   | 2           |
| mRNA catabolic process   | 2           |
| mRNA binding   | 2           |
| intrinsic apoptotic signaling pathway in response to DNA damage                                  | 2           |
| interaction with symbiont  | 2           |
| heat shock protein binding   | 2           |
| fat cell differentiation   | 2           |
| erythrocyte homeostasis  | 2           |
| erythrocyte differentiation  | 2           |
| cytosolic part   | 2           |
| cytokine metabolic process   | 2           |
| cytokine biosynthetic process  | 2           |
| cellular response to oxidative stress  | 2           |
| cellular response to molecule of bacterial origin  | 2           |
| cellular response to metal ion   | 2           |
| cellular response to lipopolysaccharide  | 2           |
| cellular response to interleukin-1   | 2           |
| cellular response to inorganic substance   | 2           |
| cellular response to calcium ion   | 2           |
| cellular response to biotic stimulus   | 2           |
| apoptotic mitochondrial changes  | 2           |
| C2vsC0   |             |
| Terms  | Z-score     |
| transcription factor binding   | 2.828427125 |
| protein domain specific binding  | 2.645751311 |
| positive regulation of cell death  | 2.449489743 |
| synapse organization   | 2.449489743 |
| regulation of anatomical structure size  | 2.449489743 |
| cell morphogenesis involved in neuron differentiation  | 2.449489743 |
| neuron projection morphogenesis  | 2.449489743 |
| plasma membrane bounded cell projection morphogenesis  | 2.449489743 |
| cell projection morphogenesis  | 2.449489743 |
| cell part morphogenesis  | 2.449489743 |
| protein kinase binding   | 2.449489743 |

# SUPPLEMENTARY DATA

|   |             |
|---|-------------|
| positive regulation of apoptotic process                              | 2.236067977 |
| positive regulation of programmed cell death                          | 2.236067977 |
| regulation of cell morphogenesis involved in differentiation          | 2.236067977 |
| regulation of cellular component size                                 | 2.236067977 |
| axonogenesis  | 2.236067977 |
| establishment of organelle localization                               | 2.236067977 |
| axon development  | 2.236067977 |
| regulation of cell morphogenesis                                      | 2.236067977 |
| organelle localization  | 2.236067977 |
| regulation of neuron projection development                           | 2.236067977 |
| negative regulation of catalytic activity                             | 2.236067977 |
| regulation of growth  | 2.236067977 |
| mRNA metabolic process  | 2.236067977 |
| inflammatory response   | 2.236067977 |
| regulation of hemopoiesis   | 2           |
| positive regulation of cell morphogenesis involved in differentiation | 2           |
| regulation of axonogenesis  | 2           |
| vesicle-mediated transport in synapse                                 | 2           |
| regulation of synapse organization                                    | 2           |
| regulation of synapse structure or activity                           | 2           |
| positive regulation of neuron projection development                  | 2           |
| postsynaptic density  | 2           |
| asymmetric synapse  | 2           |
| neuron to neuron synapse  | 2           |
| microtubule   | 2           |
| postsynaptic specialization   | 2           |
| regulation of cell growth   | 2           |
| positive regulation of neuron differentiation                         | 2           |
| positive regulation of cell projection organization                   | 2           |
| myelin sheath   | 2           |
| regulation of mRNA metabolic process                                  | 2           |
| regulation of cellular amide metabolic process                        | 2           |
| C3vsC0  |             |
| Terms   | Z-score     |
| cytosolic part  | 7.141428429 |
| ribosome  | 7           |
| ribosomal subunit   | 6.92820323  |
| amide biosynthetic process  | 6.861372412 |
| cytosolic ribosome  | 6.8556546   |
| translation   | 6.788225099 |
| peptide biosynthetic process  | 6.788225099 |
| structural constituent of ribosome                                    | 6.708203932 |
| structural molecule activity  | 6.428571429 |
| peptide metabolic process   | 6.414269806 |
| large ribosomal subunit   | 5.196152423 |
| cytosolic large ribosomal subunit                                     | 5.099019514 |
| ribonucleoprotein complex biogenesis                                  | 4.706787243 |
| small ribosomal subunit   | 4.69041576  |
| cytosolic small ribosomal subunit                                     | 4.582575695 |
| ribosome biogenesis   | 4.490731195 |
| purine ribonucleoside monophosphate metabolic process                 | 4.242640687 |
| purine nucleoside monophosphate metabolic process                     | 4.242640687 |

# SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| ribonucleoside monophosphate metabolic process           | 4.242640687 |
| nucleoside monophosphate metabolic process               | 4.242640687 |
| drug metabolic process                                   | 4.157609203 |
| ATP metabolic process                                    | 4.123105626 |
| nucleoside triphosphate metabolic process                | 4.024922359 |
| purine ribonucleotide metabolic process                  | 4.024922359 |
| ribonucleotide metabolic process                         | 4.024922359 |
| purine nucleotide metabolic process                      | 4.024922359 |
| ribose phosphate metabolic process                       | 4.024922359 |
| purine-containing compound metabolic process             | 4.024922359 |
| nucleobase-containing small molecule metabolic process   | 3.961773867 |
| purine ribonucleoside triphosphate metabolic process     | 3.900067476 |
| ribonucleoside triphosphate metabolic process            | 3.900067476 |
| purine nucleoside triphosphate metabolic process         | 3.900067476 |
| cytoplasmic translation                                  | 3.872983346 |
| ribosomal small subunit biogenesis                       | 3.872983346 |
| ribonucleoprotein complex assembly                       | 3.872983346 |
| ribonucleoprotein complex subunit organization           | 3.872983346 |
| nucleoside phosphate metabolic process                   | 3.837612894 |
| ncRNA processing   | 3.741657387 |
| ncRNA metabolic process                                  | 3.741657387 |
| rRNA binding   | 3.741657387 |
| organic cyclic compound catabolic process                | 3.709704134 |
| nucleotide metabolic process                             | 3.709704134 |
| postsynaptic specialization                              | 3.709704134 |
| rRNA processing  | 3.605551275 |
| rRNA metabolic process                                   | 3.605551275 |
| purine nucleoside monophosphate biosynthetic process     | 3.605551275 |
| purine ribonucleoside monophosphate biosynthetic process | 3.605551275 |
| ribonucleoside monophosphate biosynthetic process        | 3.605551275 |
| nucleoside monophosphate biosynthetic process            | 3.605551275 |
| cofactor biosynthetic process                            | 3.605551275 |
| generation of precursor metabolites and energy           | 3.605551275 |
| ribosome assembly  | 3.605551275 |
| postsynaptic density                                     | 3.577708764 |
| asymmetric synapse                                       | 3.577708764 |
| neuron to neuron synapse                                 | 3.577708764 |
| nucleoside diphosphate metabolic process                 | 3.464101615 |
| ATP biosynthetic process                                 | 3.464101615 |
| nucleoside phosphate catabolic process                   | 3.464101615 |
| coenzyme biosynthetic process                            | 3.464101615 |
| organophosphate catabolic process                        | 3.464101615 |
| monosaccharide metabolic process                         | 3.464101615 |
| cellular nitrogen compound catabolic process             | 3.441236008 |
| heterocycle catabolic process                            | 3.441236008 |
| aromatic compound catabolic process                      | 3.441236008 |
| cofactor metabolic process                               | 3.441236008 |
| negative regulation of intracellular signal transduction | 3.441236008 |
| purine ribonucleotide biosynthetic process               | 3.356585567 |
| ribonucleotide biosynthetic process                      | 3.356585567 |
| ribose phosphate biosynthetic process                    | 3.356585567 |
| purine nucleotide biosynthetic process                   | 3.356585567 |

## SUPPLEMENTARY DATA

|   |             |
|---|-------------|
| purine-containing compound biosynthetic process                 | 3.356585567 |
| nucleotide biosynthetic process                                 | 3.356585567 |
| nucleoside phosphate biosynthetic process                       | 3.356585567 |
| polysome  | 3.31662479  |
| ADP metabolic process   | 3.31662479  |
| nucleoside diphosphate phosphorylation                          | 3.31662479  |
| purine nucleoside diphosphate metabolic process                 | 3.31662479  |
| purine ribonucleoside diphosphate metabolic process             | 3.31662479  |
| nucleotide phosphorylation                                      | 3.31662479  |
| ribonucleoside diphosphate metabolic process                    | 3.31662479  |
| nucleotide catabolic process                                    | 3.31662479  |
| nucleobase-containing compound catabolic process                | 3.299831646 |
| homeostasis of number of cells                                  | 3.299831646 |
| carbohydrate catabolic process                                  | 3.207134903 |
| purine ribonucleoside triphosphate biosynthetic process         | 3.207134903 |
| purine nucleoside triphosphate biosynthetic process             | 3.207134903 |
| ribonucleoside triphosphate biosynthetic process                | 3.207134903 |
| nucleoside triphosphate biosynthetic process                    | 3.207134903 |
| nucleobase-containing small molecule biosynthetic process       | 3.207134903 |
| coenzyme metabolic process                                      | 3.207134903 |
| polysomal ribosome  | 3.16227766  |
| glycolytic process  | 3.16227766  |
| ATP generation from ADP   | 3.16227766  |
| pyruvate biosynthetic process                                   | 3.16227766  |
| nicotinamide nucleotide biosynthetic process                    | 3.16227766  |
| pyridine nucleotide biosynthetic process                        | 3.16227766  |
| pyridine-containing compound biosynthetic process               | 3.16227766  |
| hexose metabolic process  | 3.16227766  |
| response to interferon-gamma                                    | 3.16227766  |
| cytokine activity   | 3.16227766  |
| carbohydrate metabolic process                                  | 3.130495168 |
| regulation of neuron death                                      | 3.130495168 |
| neuron death  | 3.127716211 |
| postsynapse   | 3.127716211 |
| regulation of ERK1 and ERK2 cascade                             | 3.050851079 |
| ERK1 and ERK2 cascade   | 3.050851079 |
| myeloid cell homeostasis  | 3.050851079 |
| glucose metabolic process                                       | 3           |
| ribosomal small subunit assembly                                | 3           |
| ribosomal large subunit biogenesis                              | 3           |
| apoptotic signaling pathway                                     | 3           |
| carbohydrate derivative biosynthetic process                    | 2.98240454  |
| amide binding   | 2.98240454  |
| myeloid cell differentiation                                    | 2.98240454  |
| pyruvate metabolic process                                      | 2.886751346 |
| nicotinamide nucleotide metabolic process                       | 2.886751346 |
| pyridine nucleotide metabolic process                           | 2.886751346 |
| pyridine-containing compound metabolic process                  | 2.886751346 |
| oxidoreduction coenzyme metabolic process                       | 2.886751346 |
| intrinsic apoptotic signaling pathway in response to DNA damage | 2.886751346 |
| erythrocyte homeostasis   | 2.886751346 |
| negative regulation of apoptotic signaling pathway              | 2.840187787 |

# SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| organophosphate biosynthetic process                         | 2.836832573 |
| regulation of MAPK cascade                                   | 2.836832573 |
| monocarboxylic acid biosynthetic process                     | 2.828427125 |
| carbohydrate biosynthetic process                            | 2.828427125 |
| vacuolar membrane  | 2.828427125 |
| vacuolar part  | 2.828427125 |
| response to tumor necrosis factor                            | 2.828427125 |
| regulation of apoptotic signaling pathway                    | 2.828427125 |
| mitochondrial outer membrane                                 | 2.828427125 |
| outer membrane   | 2.828427125 |
| organelle outer membrane                                     | 2.828427125 |
| peptide binding  | 2.828427125 |
| small molecule biosynthetic process                          | 2.785430073 |
| MAPK cascade   | 2.710687383 |
| regulation of cytokine production                            | 2.69407953  |
| positive regulation of cell death                            | 2.69407953  |
| neuron apoptotic process                                     | 2.667891875 |
| monosaccharide biosynthetic process                          | 2.645751311 |
| cellular response to interferon-gamma                        | 2.645751311 |
| regulation of response to external stimulus                  | 2.611164839 |
| regulation of cellular response to stress                    | 2.558408596 |
| granulocyte chemotaxis                                       | 2.529822128 |
| granulocyte migration  | 2.529822128 |
| positive regulation of ERK1 and ERK2 cascade                 | 2.529822128 |
| negative regulation of intrinsic apoptotic signaling pathway | 2.529822128 |
| lysosomal membrane   | 2.449489743 |
| lytic vacuole membrane                                       | 2.449489743 |
| chemokine receptor binding                                   | 2.449489743 |
| regulation of fibroblast proliferation                       | 2.449489743 |
| fibroblast proliferation                                     | 2.449489743 |
| positive regulation of cell migration                        | 2.449489743 |
| positive regulation of cell motility                         | 2.449489743 |
| positive regulation of cellular component movement           | 2.449489743 |
| positive regulation of locomotion                            | 2.449489743 |
| negative regulation of transport                             | 2.449489743 |
| vacuole  | 2.414039396 |
| inflammatory response  | 2.400980192 |
| monocarboxylic acid metabolic process                        | 2.400396793 |
| negative regulation of response to external stimulus         | 2.357022604 |
| intrinsic apoptotic signaling pathway                        | 2.357022604 |
| neutrophil chemotaxis  | 2.333333333 |
| neutrophil migration   | 2.333333333 |
| positive regulation of myeloid cell differentiation          | 2.333333333 |
| regulation of myeloid leukocyte differentiation              | 2.333333333 |
| negative regulation of neuron death                          | 2.323790008 |
| regulation of neuron apoptotic process                       | 2.323790008 |
| regulation of myeloid cell differentiation                   | 2.323790008 |
| regulation of intrinsic apoptotic signaling pathway          | 2.309401077 |
| carboxylic acid biosynthetic process                         | 2.293658555 |
| organic acid biosynthetic process                            | 2.293658555 |
| leukocyte migration  | 2.293658555 |
| positive regulation of cytokine production                   | 2.293658555 |

# SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| lysosome   | 2.267786838 |
| lytic vacuole  | 2.267786838 |
| peptide secretion  | 2.267786838 |
| positive regulation of programmed cell death   | 2.267786838 |
| cytokine production  | 2.263009527 |
| maturation of SSU-rRNA   | 2.236067977 |
| large ribosomal subunit rRNA binding   | 2.236067977 |
| cellular aldehyde metabolic process  | 2.236067977 |
| gluconeogenesis  | 2.236067977 |
| hexose biosynthetic process  | 2.236067977 |
| regulation of ATP metabolic process  | 2.236067977 |
| ribosomal large subunit assembly   | 2.236067977 |
| chemokine activity   | 2.236067977 |
| CCR chemokine receptor binding   | 2.236067977 |
| lymphocyte chemotaxis  | 2.236067977 |
| response to chemokine  | 2.236067977 |
| cellular response to chemokine   | 2.236067977 |
| positive regulation of fibroblast proliferation  | 2.236067977 |
| leukocyte chemotaxis   | 2.182820625 |
| myeloid leukocyte differentiation  | 2.138089935 |
| leukocyte differentiation  | 2.132007164 |
| positive regulation of myeloid leukocyte differentiation                                 | 2.121320344 |
| osteoclast differentiation   | 2.121320344 |
| regulation of peptide secretion  | 2.116950987 |
| protein secretion  | 2.116950987 |
| positive regulation of apoptotic process   | 2.116950987 |
| mononuclear cell migration   | 2.110579412 |
| myeloid leukocyte migration  | 2.064741605 |
| regulation of hemopoiesis  | 2.064741605 |
| regulation of establishment of protein localization                                      | 2.04264872  |
| regulation of peptide transport  | 2.04264872  |
| maturation of SSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA) | 2           |
| regulation of glycolytic process   | 2           |
| regulation of nucleotide catabolic process   | 2           |
| regulation of carbohydrate catabolic process   | 2           |
| regulation of coenzyme metabolic process   | 2           |
| cellular response to interleukin-4   | 2           |
| response to interleukin-4  | 2           |
| eosinophil chemotaxis  | 2           |
| eosinophil migration   | 2           |
| BH domain binding  | 2           |
| myeloid leukocyte cytokine production  | 2           |
| positive regulation of cytokine production involved in immune response                   | 2           |
| C4vsC0   |             |
| Terms  | Z-score     |
| modulation of chemical synaptic transmission   | 3.16227766  |
| regulation of trans-synaptic signaling   | 3.16227766  |
| dendrite   | 3.16227766  |
| dendritic tree   | 3.16227766  |
| positive regulation of synaptic transmission   | 3           |
| axon   | 3           |
| inorganic molecular entity transmembrane transporter activity                            | 3           |

# SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| glial cell differentiation                                     | 2.828427125 |
| synapse organization   | 2.828427125 |
| inorganic cation transmembrane transporter activity            | 2.828427125 |
| cation transmembrane transporter activity                      | 2.828427125 |
| postsynapse  | 2.828427125 |
| behavior   | 2.713602101 |
| learning or memory   | 2.645751311 |
| cognition  | 2.645751311 |
| cell projection morphogenesis                                  | 2.645751311 |
| cell part morphogenesis  | 2.645751311 |
| axon part  | 2.645751311 |
| amide binding  | 2.645751311 |
| peptide metabolic process                                      | 2.645751311 |
| monovalent inorganic cation transmembrane transporter activity | 2.645751311 |
| response to inorganic substance                                | 2.645751311 |
| mitochondrial membrane   | 2.645751311 |
| mitochondrial envelope   | 2.645751311 |
| generation of precursor metabolites and energy                 | 2.645751311 |
| positive regulation of cell death                              | 2.645751311 |
| regulation of MAPK cascade                                     | 2.645751311 |
| MAPK cascade   | 2.645751311 |
| glutamatergic synapse  | 2.645751311 |
| presynapse   | 2.645751311 |
| gliogenesis  | 2.529822128 |
| neuronal cell body   | 2.529822128 |
| negative regulation of nervous system development              | 2.449489743 |
| regulation of synapse organization                             | 2.449489743 |
| regulation of synapse structure or activity                    | 2.449489743 |
| regulation of synaptic plasticity                              | 2.449489743 |
| cell morphogenesis involved in neuron differentiation          | 2.449489743 |
| neuron projection morphogenesis                                | 2.449489743 |
| plasma membrane bounded cell projection morphogenesis          | 2.449489743 |
| distal axon  | 2.449489743 |
| peptide binding  | 2.449489743 |
| protein homo-oligomerization                                   | 2.449489743 |
| negative regulation of phosphorylation                         | 2.449489743 |
| negative regulation of phosphorus metabolic process            | 2.449489743 |
| negative regulation of phosphate metabolic process             | 2.449489743 |
| protein complex oligomerization                                | 2.449489743 |
| neurotransmitter transport                                     | 2.449489743 |
| anion transport  | 2.449489743 |
| response to toxic substance                                    | 2.449489743 |
| positive regulation of transmembrane transport                 | 2.449489743 |
| mitochondrial inner membrane                                   | 2.449489743 |
| organelle inner membrane                                       | 2.449489743 |
| small molecule biosynthetic process                            | 2.449489743 |
| positive regulation of apoptotic process                       | 2.449489743 |
| positive regulation of programmed cell death                   | 2.449489743 |
| regulation of ERK1 and ERK2 cascade                            | 2.449489743 |
| ERK1 and ERK2 cascade  | 2.449489743 |
| regulation of transmembrane transport                          | 2.333333333 |
| cellular metal ion homeostasis                                 | 2.333333333 |

# SUPPLEMENTARY DATA

|   |             |
|---|-------------|
| cellular cation homeostasis                           | 2.333333333 |
| cellular ion homeostasis                              | 2.333333333 |
| metal ion homeostasis                                 | 2.333333333 |
| cation homeostasis                                    | 2.333333333 |
| inorganic ion homeostasis                             | 2.333333333 |
| drug metabolic process                                | 2.333333333 |
| glial cell development                                | 2.236067977 |
| negative regulation of neurogenesis                   | 2.236067977 |
| negative regulation of cell development               | 2.236067977 |
| long-term synaptic potentiation                       | 2.236067977 |
| regulation of cell morphogenesis                      | 2.236067977 |
| growth cone   | 2.236067977 |
| site of polarized growth                              | 2.236067977 |
| aging   | 2.236067977 |
| sulfur compound binding                               | 2.236067977 |
| negative regulation of protein phosphorylation        | 2.236067977 |
| import across plasma membrane                         | 2.236067977 |
| metal ion transmembrane transporter activity          | 2.236067977 |
| positive regulation of cation transmembrane transport | 2.236067977 |
| positive regulation of ion transmembrane transport    | 2.236067977 |
| ATP metabolic process                                 | 2.236067977 |
| purine ribonucleoside monophosphate metabolic process | 2.236067977 |
| purine ribonucleoside triphosphate metabolic process  | 2.236067977 |
| purine nucleoside monophosphate metabolic process     | 2.236067977 |
| ribonucleoside monophosphate metabolic process        | 2.236067977 |
| ribonucleoside triphosphate metabolic process         | 2.236067977 |
| purine nucleoside triphosphate metabolic process      | 2.236067977 |
| nucleoside monophosphate metabolic process            | 2.236067977 |
| nucleoside triphosphate metabolic process             | 2.236067977 |
| carboxylic acid biosynthetic process                  | 2.236067977 |
| organic acid biosynthetic process                     | 2.236067977 |
| purine ribonucleotide metabolic process               | 2.236067977 |
| ribonucleotide metabolic process                      | 2.236067977 |
| purine nucleotide metabolic process                   | 2.236067977 |
| ribose phosphate metabolic process                    | 2.236067977 |
| purine-containing compound metabolic process          | 2.236067977 |
| cofactor metabolic process                            | 2.236067977 |
| positive regulation of MAPK cascade                   | 2.236067977 |
| synaptic membrane                                     | 2.236067977 |
| regulation of cellular protein localization           | 2.236067977 |
| regulation of cation transmembrane transport          | 2.121320344 |
| regulation of ion transmembrane transport             | 2.121320344 |
| regulation of neurotransmitter levels                 | 2.121320344 |
| cellular divalent inorganic cation homeostasis        | 2.121320344 |
| divalent inorganic cation homeostasis                 | 2.121320344 |
| perinuclear region of cytoplasm                       | 2.121320344 |
| cell body   | 2.110579412 |
| regulation of ion transport                           | 2.110579412 |
| astrocyte differentiation                             | 2           |
| oligodendrocyte differentiation                       | 2           |
| memory  | 2           |
| regulation of calcium ion transmembrane transport     | 2           |

# SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| postsynapse organization   | 2           |
| neurotransmitter uptake  | 2           |
| sodium ion transmembrane transporter activity                      | 2           |
| dendritic spine  | 2           |
| neuron spine   | 2           |
| response to light stimulus   | 2           |
| carboxylic acid transport  | 2           |
| organic acid transport   | 2           |
| detoxification   | 2           |
| cellular response to metal ion                                     | 2           |
| cellular response to inorganic substance                           | 2           |
| response to metal ion  | 2           |
| positive regulation of ion transmembrane transporter activity      | 2           |
| positive regulation of transporter activity                        | 2           |
| mitochondrial transport  | 2           |
| energy derivation by oxidation of organic compounds                | 2           |
| monocarboxylic acid biosynthetic process                           | 2           |
| antioxidant activity   | 2           |
| cellular lipid catabolic process                                   | 2           |
| lipid catabolic process  | 2           |
| positive regulation of ERK1 and ERK2 cascade                       | 2           |
| regulation of blood pressure                                       | 2           |
| C5vsC0   |             |
| Terms  | Z-score     |
| defense response to other organism                                 | 3.464101615 |
| response to virus  | 3.31662479  |
| defense response to virus  | 3.16227766  |
| interspecies interaction between organisms                         | 3.16227766  |
| regulation of cytokine production                                  | 3           |
| cytokine production  | 3           |
| viral process  | 2.828427125 |
| symbiont process   | 2.828427125 |
| cytokine-mediated signaling pathway                                | 2.828427125 |
| regulation of viral process  | 2.645751311 |
| regulation of symbiosis, encompassing mutualism through parasitism | 2.645751311 |
| regulation of multi-organism process                               | 2.645751311 |
| response to interferon-gamma                                       | 2.645751311 |
| regulation of defense response                                     | 2.645751311 |
| positive regulation of immune response                             | 2.645751311 |
| negative regulation of viral process                               | 2.449489743 |
| negative regulation of multi-organism process                      | 2.449489743 |
| response to interferon-beta  | 2.449489743 |
| negative regulation of cellular component organization             | 2.449489743 |
| positive regulation of cytokine production                         | 2.449489743 |
| negative regulation of cell proliferation                          | 2.449489743 |
| regulation of viral life cycle                                     | 2.236067977 |
| viral life cycle   | 2.236067977 |
| cellular response to interferon-gamma                              | 2.236067977 |
| G protein-coupled receptor binding                                 | 2.236067977 |
| positive regulation of hydrolase activity                          | 2.236067977 |
| response to type I interferon                                      | 2.236067977 |
| regulation of innate immune response                               | 2.236067977 |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| regulation of immune effector process                  | 2.236067977 |
| myeloid cell homeostasis                               | 2.236067977 |
| homeostasis of number of cells                         | 2.236067977 |
| myeloid cell differentiation                           | 2.236067977 |
| negative regulation of viral genome replication        | 2           |
| negative regulation of viral life cycle                | 2           |
| regulation of viral genome replication                 | 2           |
| viral genome replication                               | 2           |
| response to interferon-alpha                           | 2           |
| CCR chemokine receptor binding                         | 2           |
| monocyte chemotaxis                                    | 2           |
| chemokine receptor binding                             | 2           |
| response to chemokine                                  | 2           |
| cellular response to chemokine                         | 2           |
| mononuclear cell migration                             | 2           |
| regulation of leukocyte chemotaxis                     | 2           |
| cellular response to tumor necrosis factor             | 2           |
| response to tumor necrosis factor                      | 2           |
| leukocyte chemotaxis                                   | 2           |
| cell chemotaxis  | 2           |
| regulation of ERK1 and ERK2 cascade                    | 2           |
| cytokine receptor binding                              | 2           |
| ERK1 and ERK2 cascade                                  | 2           |
| regulation of epithelial cell proliferation            | 2           |
| response to molecule of bacterial origin               | 2           |
| epithelial cell proliferation                          | 2           |
| type I interferon signaling pathway                    | 2           |
| cellular response to type I interferon                 | 2           |
| positive regulation of innate immune response          | 2           |
| positive regulation of defense response                | 2           |
| positive regulation of leukocyte mediated cytotoxicity | 2           |
| positive regulation of cell killing                    | 2           |
| regulation of leukocyte mediated cytotoxicity          | 2           |
| regulation of cell killing                             | 2           |
| leukocyte mediated cytotoxicity                        | 2           |
| cell killing   | 2           |
| regulation of adaptive immune response                 | 2           |
| positive regulation of immune effector process         | 2           |
| lymphocyte mediated immunity                           | 2           |
| erythrocyte differentiation                            | 2           |
| erythrocyte homeostasis                                | 2           |
| regulation of myeloid cell differentiation             | 2           |
| regulation of hemopoiesis                              | 2           |

**Supplementary Table 3.** Functional enrichment results of DEGs for HAM in whole brain.

| Substance and energy metabolism |            |
|---------------------------------|------------|
| Terms                           | Z-score    |
| amide biosynthetic process      | 6.32455532 |
| peptide biosynthetic process    | 6.32455532 |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| peptide metabolic process                                | 5.813776741 |
| organic cyclic compound catabolic process                | 4.024922359 |
| drug metabolic process                                   | 3.77964473  |
| aromatic compound catabolic process                      | 3.771236166 |
| cellular nitrogen compound catabolic process             | 3.771236166 |
| heterocycle catabolic process                            | 3.771236166 |
| nucleobase-containing compound catabolic process         | 3.638034376 |
| nucleoside monophosphate metabolic process               | 3.638034376 |
| purine nucleoside monophosphate metabolic process        | 3.638034376 |
| purine ribonucleoside monophosphate metabolic process    | 3.638034376 |
| ribonucleoside monophosphate metabolic process           | 3.638034376 |
| ATP metabolic process                                    | 3.5         |
| nucleoside triphosphate metabolic process                | 3.441236008 |
| purine nucleotide metabolic process                      | 3.441236008 |
| purine ribonucleotide metabolic process                  | 3.441236008 |
| purine-containing compound metabolic process             | 3.441236008 |
| ribonucleotide metabolic process                         | 3.441236008 |
| ribose phosphate metabolic process                       | 3.441236008 |
| cofactor biosynthetic process                            | 3.31662479  |
| nucleoside diphosphate metabolic process                 | 3.31662479  |
| nucleoside monophosphate biosynthetic process            | 3.31662479  |
| nucleoside phosphate catabolic process                   | 3.31662479  |
| organophosphate catabolic process                        | 3.31662479  |
| purine nucleoside monophosphate biosynthetic process     | 3.31662479  |
| purine ribonucleoside monophosphate biosynthetic process | 3.31662479  |
| ribonucleoside monophosphate biosynthetic process        | 3.31662479  |
| purine nucleoside triphosphate metabolic process         | 3.299831646 |
| purine ribonucleoside triphosphate metabolic process     | 3.299831646 |
| ribonucleoside triphosphate metabolic process            | 3.299831646 |
| nucleobase-containing small molecule metabolic process   | 3.273268354 |
| nucleoside phosphate metabolic process                   | 3.273268354 |
| generation of precursor metabolites and energy           | 3.207134903 |
| ADP metabolic process                                    | 3.16227766  |
| ATP biosynthetic process                                 | 3.16227766  |
| coenzyme biosynthetic process                            | 3.16227766  |
| monosaccharide metabolic process                         | 3.16227766  |
| nucleotide catabolic process                             | 3.16227766  |
| purine nucleoside diphosphate metabolic process          | 3.16227766  |
| purine ribonucleoside diphosphate metabolic process      | 3.16227766  |

## SUPPLEMENTARY DATA

|   |             |
|---|-------------|
| ribonucleoside diphosphate metabolic process              | 3.16227766  |
| nucleotide metabolic process                              | 3.130495168 |
| carbohydrate catabolic process                            | 3.050851079 |
| coenzyme metabolic process                                | 3.050851079 |
| nucleobase-containing small molecule biosynthetic process | 3.050851079 |
| nucleoside phosphate biosynthetic process                 | 3.050851079 |
| nucleotide biosynthetic process                           | 3.050851079 |
| purine nucleotide biosynthetic process                    | 3.050851079 |
| purine ribonucleotide biosynthetic process                | 3.050851079 |
| purine-containing compound biosynthetic process           | 3.050851079 |
| ribonucleotide biosynthetic process                       | 3.050851079 |
| ribose phosphate biosynthetic process                     | 3.050851079 |
| ATP generation from ADP                                   | 3           |
| glycolytic process  | 3           |
| hexose metabolic process                                  | 3           |
| nicotinamide nucleotide biosynthetic process              | 3           |
| pyridine nucleotide biosynthetic process                  | 3           |
| pyridine-containing compound biosynthetic process         | 3           |
| pyruvate biosynthetic process                             | 3           |
| cofactor metabolic process                                | 2.98240454  |
| nucleoside triphosphate biosynthetic process              | 2.886751346 |
| purine nucleoside triphosphate biosynthetic process       | 2.886751346 |
| purine ribonucleoside triphosphate biosynthetic process   | 2.886751346 |
| ribonucleoside triphosphate biosynthetic process          | 2.886751346 |
| carbohydrate metabolic process                            | 2.828427125 |
| glucose metabolic process                                 | 2.828427125 |
| nicotinamide nucleotide metabolic process                 | 2.713602101 |
| oxidoreduction coenzyme metabolic process                 | 2.713602101 |
| pyridine nucleotide metabolic process                     | 2.713602101 |
| pyridine-containing compound metabolic process            | 2.713602101 |
| pyruvate metabolic process                                | 2.713602101 |
| organophosphate biosynthetic process                      | 2.523573073 |
| monocarboxylic acid biosynthetic process                  | 2.5         |
| monosaccharide biosynthetic process                       | 2.449489743 |
| monocarboxylic acid metabolic process                     | 2.357022604 |
| small molecule biosynthetic process                       | 2.353393622 |
| cellular aldehyde metabolic process                       | 2.236067977 |
| gluconeogenesis   | 2.236067977 |
| hexose biosynthetic process                               | 2.236067977 |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| negative regulation of lipid metabolic process                 | 2.236067977 |
| regulation of ATP biosynthetic process                         | 2           |
| regulation of carbohydrate catabolic process                   | 2           |
| regulation of coenzyme metabolic process                       | 2           |
| regulation of glycolytic process                               | 2           |
| regulation of nucleotide catabolic process                     | 2           |
| Chemotaxis   |             |
| Terms  | Z-score     |
| CCR chemokine receptor binding                                 | 2.236067977 |
| cell chemotaxis  | 2.293658555 |
| chemokine activity   | 2.449489743 |
| chemokine receptor binding                                     | 2.645751311 |
| chemokine-mediated signaling pathway                           | 2           |
| chemotaxis   | 2.04264872  |
| eosinophil chemotaxis  | 2           |
| eosinophil migration   | 2           |
| granulocyte chemotaxis   | 2.529822128 |
| granulocyte migration  | 2.529822128 |
| leukocyte chemotaxis   | 2.357022604 |
| leukocyte migration  | 2.449489743 |
| lymphocyte chemotaxis  | 2.449489743 |
| mononuclear cell migration                                     | 2.110579412 |
| myeloid leukocyte migration                                    | 2.064741605 |
| neutrophil chemotaxis  | 2.333333333 |
| neutrophil migration   | 2.333333333 |
| positive regulation of blood vessel endothelial cell migration | 2           |
| positive regulation of cell migration                          | 2.745625892 |
| positive regulation of cell motility                           | 2.745625892 |
| positive regulation of cellular component movement             | 2.745625892 |
| positive regulation of locomotion                              | 2.745625892 |
| regulation of leukocyte migration                              | 2.138089935 |
| taxis  | 2.19089023  |
| Ribosome activity  |             |
| Terms  | Z-score     |
| cytoplasmic translation  | 3.16227766  |
| cytosolic large ribosomal subunit                              | 4           |
| cytosolic ribosome   | 5.830951895 |
| cytosolic small ribosomal subunit                              | 4.242640687 |
| large ribosomal subunit  | 4.123105626 |

## SUPPLEMENTARY DATA

|   |             |
|---|-------------|
| large ribosomal subunit rRNA binding                            | 2           |
| polysomal ribosome  | 2.236067977 |
| polysome  | 2.449489743 |
| ribonucleoprotein complex assembly                              | 3.16227766  |
| ribonucleoprotein complex biogenesis                            | 3.900067476 |
| ribonucleoprotein complex subunit organization                  | 3.16227766  |
| ribosomal small subunit assembly                                | 2.645751311 |
| ribosomal small subunit biogenesis                              | 3.31662479  |
| ribosomal subunit   | 5.916079783 |
| ribosome  | 6           |
| ribosome assembly   | 3           |
| ribosome biogenesis   | 3.771236166 |
| rRNA binding  | 3           |
| small ribosomal subunit   | 4.358898944 |
| structural constituent of ribosome                              | 5.830951895 |
| translation   | 6.32455532  |
| Cell survival   |             |
| Terms   | Z-score     |
| regulation of neuron death                                      | 3.273268354 |
| apoptotic signaling pathway                                     | 3.265986324 |
| neuron death  | 3.265986324 |
| positive regulation of cell death                               | 3.023715784 |
| negative regulation of apoptotic signaling pathway              | 2.840187787 |
| neuron apoptotic process  | 2.828427125 |
| regulation of apoptotic signaling pathway                       | 2.828427125 |
| intrinsic apoptotic signaling pathway in response to DNA damage | 2.713602101 |
| negative regulation of neuron death                             | 2.667891875 |
| positive regulation of programmed cell death                    | 2.6         |
| intrinsic apoptotic signaling pathway                           | 2.5         |
| regulation of neuron apoptotic process                          | 2.5         |
| positive regulation of apoptotic process                        | 2.449489743 |
| regulation of leukocyte apoptotic process                       | 2.334868926 |
| negative regulation of intrinsic apoptotic signaling pathway    | 2.333333333 |
| regulation of intrinsic apoptotic signaling pathway             | 2.110579412 |
| Cellular response to stimulus                                   |             |
| Terms   | Z-score     |
| cellular response to chemokine                                  | 2.236067977 |
| cellular response to interferon-gamma                           | 2.645751311 |
| cellular response to lipoprotein particle stimulus              | 2           |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| DNA damage response, signal transduction by p53 class mediator | 2           |
| negative regulation of response to external stimulus           | 2.828427125 |
| negative regulation of response to wounding                    | 2.449489743 |
| regulation of cellular response to stress                      | 2.683281573 |
| regulation of response to external stimulus                    | 3.211586168 |
| regulation of response to wounding                             | 2.828427125 |
| response to chemokine  | 2.236067977 |
| response to interferon-gamma                                   | 3.16227766  |
| response to lipoprotein particle                               | 2           |
| response to tumor necrosis factor                              | 2.828427125 |
| response to wounding   | 4.146139914 |
| Coagulation and hemostasis                                     |             |
| Terms  | Z-score     |
| blood coagulation  | 2.713602101 |
| coagulation  | 2.713602101 |
| hemostasis   | 2.713602101 |
| negative regulation of blood coagulation                       | 2.236067977 |
| negative regulation of coagulation                             | 2.236067977 |
| negative regulation of hemostasis                              | 2.236067977 |
| negative regulation of wound healing                           | 2.449489743 |
| platelet activation  | 2.121320344 |
| regulation of blood coagulation                                | 2.449489743 |
| regulation of coagulation                                      | 2.449489743 |
| regulation of hemostasis                                       | 2.449489743 |
| regulation of platelet activation                              | 2           |
| regulation of wound healing                                    | 2.645751311 |
| wound healing  | 3.5         |
| Immunity and inflammation                                      |             |
| Terms  | Z-score     |
| inflammatory response  | 2.743977362 |
| leukocyte differentiation                                      | 2.558408596 |
| myeloid cell differentiation                                   | 3.441236008 |
| myeloid leukocyte differentiation                              | 2.496150883 |
| negative regulation of immune system process                   | 3.130495168 |
| positive regulation of leukocyte differentiation               | 3.271651525 |
| positive regulation of myeloid cell differentiation            | 2.333333333 |
| positive regulation of myeloid leukocyte differentiation       | 2.121320344 |
| regulation of leukocyte differentiation                        | 2.138089935 |
| regulation of myeloid cell differentiation                     | 2.672612419 |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| regulation of myeloid leukocyte differentiation                        | 2.333333333 |
| Cytokine secretion   |             |
| Terms  | Z-score     |
| cytokine activity  | 3.31662479  |
| cytokine production  | 2.263009527 |
| cytokine-mediated signaling pathway                                    | 2.138089935 |
| myeloid leukocyte cytokine production                                  | 2           |
| positive regulation of cytokine production                             | 2.293658555 |
| positive regulation of cytokine production involved in immune response | 2           |
| regulation of cytokine production                                      | 2.69407953  |

**Supplementary Table 4.** Functional enrichment results of DEGs for age-associated microglia in subependymal ventricular zone.

|  |             |
|--|-------------|
| Substance and energy metabolism                                  |             |
| Terms  | Z-score     |
| ADP metabolic process  | 3           |
| ATP metabolic process  | 3.741657387 |
| carbohydrate metabolic process                                   | 3.638034376 |
| coenzyme metabolic process                                       | 3.16227766  |
| cofactor metabolic process                                       | 4.358898944 |
| drug metabolic process   | 5           |
| generation of precursor metabolites and energy                   | 3.464101615 |
| glucose metabolic process  | 2.828427125 |
| hexose metabolic process   | 3           |
| monocarboxylic acid metabolic process                            | 4           |
| monosaccharide metabolic process                                 | 3           |
| neurotransmitter metabolic process                               | 2.449489743 |
| nicotinamide nucleotide metabolic process                        | 3           |
| nitric oxide metabolic process                                   | 2.449489743 |
| nucleobase-containing small molecule metabolic process           | 4           |
| nucleoside diphosphate metabolic process                         | 3.16227766  |
| nucleoside monophosphate metabolic process                       | 3.741657387 |
| nucleoside phosphate metabolic process                           | 4           |
| nucleoside triphosphate metabolic process                        | 4           |
| nucleotide metabolic process                                     | 3.872983346 |
| oxidoreduction coenzyme metabolic process                        | 3           |
| positive regulation of reactive oxygen species metabolic process | 2.645751311 |

## SUPPLEMENTARY DATA

|   |             |
|---|-------------|
| purine nucleoside diphosphate metabolic process         | 3           |
| purine nucleoside monophosphate metabolic process       | 3.741657387 |
| purine nucleoside triphosphate metabolic process        | 3.872983346 |
| purine nucleotide metabolic process                     | 3.872983346 |
| purine ribonucleoside diphosphate metabolic process     | 3           |
| purine ribonucleoside monophosphate metabolic process   | 3.741657387 |
| purine ribonucleoside triphosphate metabolic process    | 3.872983346 |
| purine ribonucleotide metabolic process                 | 3.872983346 |
| purine-containing compound metabolic process            | 3.872983346 |
| pyridine nucleotide metabolic process                   | 3           |
| pyridine-containing compound metabolic process          | 3           |
| pyruvate metabolic process                              | 3           |
| reactive nitrogen species metabolic process             | 2.449489743 |
| reactive oxygen species metabolic process               | 3.872983346 |
| regulation of ATP metabolic process                     | 2.236067977 |
| regulation of coenzyme metabolic process                | 2           |
| regulation of cofactor metabolic process                | 2.236067977 |
| regulation of nucleotide metabolic process              | 2.236067977 |
| regulation of purine nucleotide metabolic process       | 2.236067977 |
| regulation of reactive oxygen species metabolic process | 3.31662479  |
| ribonucleoside diphosphate metabolic process            | 3           |
| ribonucleoside monophosphate metabolic process          | 3.741657387 |
| ribonucleoside triphosphate metabolic process           | 3.872983346 |
| ribonucleotide metabolic process                        | 3.872983346 |
| ribose phosphate metabolic process                      | 3.872983346 |
| aromatic compound catabolic process                     | 3.900067476 |
| carbohydrate catabolic process                          | 2.529822128 |
| cellular nitrogen compound catabolic process            | 3.900067476 |
| heterocycle catabolic process                           | 3.900067476 |
| nucleobase-containing compound catabolic process        | 3.638034376 |
| nucleoside phosphate catabolic process                  | 3.16227766  |
| nucleotide catabolic process                            | 3           |
| organic cyclic compound catabolic process               | 4.146139914 |
| organophosphate catabolic process                       | 3.16227766  |
| regulation of carbohydrate catabolic process            | 2           |
| regulation of nucleotide catabolic process              | 2           |
| ATP biosynthetic process                                | 3           |
| carbohydrate biosynthetic process                       | 2.828427125 |
| carbohydrate derivative biosynthetic process            | 3.356585567 |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| carboxylic acid biosynthetic process                       | 3.605551275 |
| coenzyme biosynthetic process                              | 3           |
| cofactor biosynthetic process                              | 3.605551275 |
| hexose biosynthetic process                                | 2.236067977 |
| monocarboxylic acid biosynthetic process                   | 3.464101615 |
| monosaccharide biosynthetic process                        | 2.236067977 |
| neurotransmitter biosynthetic process                      | 2.236067977 |
| nicotinamide nucleotide biosynthetic process               | 3           |
| nitric oxide biosynthetic process                          | 2.236067977 |
| nucleobase-containing small molecule biosynthetic process  | 3.31662479  |
| nucleoside monophosphate biosynthetic process              | 3           |
| nucleoside phosphate biosynthetic process                  | 3.16227766  |
| nucleoside triphosphate biosynthetic process               | 3.16227766  |
| nucleotide biosynthetic process                            | 3.16227766  |
| organic acid biosynthetic process                          | 3.605551275 |
| organophosphate biosynthetic process                       | 3.356585567 |
| purine nucleoside monophosphate biosynthetic process       | 3           |
| purine nucleoside triphosphate biosynthetic process        | 3.16227766  |
| purine nucleotide biosynthetic process                     | 3.16227766  |
| purine ribonucleoside monophosphate biosynthetic process   | 3           |
| purine ribonucleoside triphosphate biosynthetic process    | 3.16227766  |
| purine ribonucleotide biosynthetic process                 | 3.16227766  |
| purine-containing compound biosynthetic process            | 3.16227766  |
| pyridine nucleotide biosynthetic process                   | 3           |
| pyridine-containing compound biosynthetic process          | 3           |
| pyruvate biosynthetic process                              | 3           |
| reactive oxygen species biosynthetic process               | 2.645751311 |
| regulation of ATP biosynthetic process                     | 2           |
| regulation of nitric oxide biosynthetic process            | 2           |
| regulation of reactive oxygen species biosynthetic process | 2.236067977 |
| ribonucleoside monophosphate biosynthetic process          | 3           |
| ribonucleoside triphosphate biosynthetic process           | 3.16227766  |
| ribonucleotide biosynthetic process                        | 3.16227766  |
| ribose phosphate biosynthetic process                      | 3.16227766  |
| small molecule biosynthetic process                        | 4.242640687 |
| ATP generation from ADP                                    | 3           |
| gluconeogenesis  | 2.236067977 |
| glycolytic process   | 3           |
| regulation of glycolytic process                           | 2           |

## SUPPLEMENTARY DATA

| Cytokine secretion   |             |
|--|-------------|
| Terms  | Z-score     |
| cytokine production  | 5.567764363 |
| cytokine secretion   | 3.31662479  |
| negative regulation of cytokine production                                   | 3.31662479  |
| negative regulation of tumor necrosis factor superfamily cytokine production | 2           |
| positive regulation of cytokine production                                   | 4.358898944 |
| positive regulation of cytokine secretion                                    | 3           |
| positive regulation of tumor necrosis factor superfamily cytokine production | 2.645751311 |
| regulation of cytokine production  | 5.291502622 |
| regulation of cytokine secretion   | 3.16227766  |
| regulation of tumor necrosis factor superfamily cytokine production          | 3.31662479  |
| tumor necrosis factor superfamily cytokine production                        | 3.464101615 |
| interleukin-1 beta production  | 2.645751311 |
| interleukin-1 beta secretion   | 2           |
| interleukin-1 production   | 2.645751311 |
| interleukin-1 secretion  | 2           |
| negative regulation of tumor necrosis factor production                      | 2           |
| positive regulation of interleukin-1 beta production                         | 2.236067977 |
| positive regulation of interleukin-1 production                              | 2.236067977 |
| positive regulation of interleukin-6 production                              | 2.236067977 |
| positive regulation of tumor necrosis factor production                      | 2.645751311 |
| regulation of interleukin-1 beta production                                  | 2.449489743 |
| regulation of interleukin-1 production                                       | 2.449489743 |
| peptide secretion  | 4.146139914 |
| positive regulation of peptide secretion                                     | 3.207134903 |
| positive regulation of protein secretion                                     | 3.207134903 |
| positive regulation of secretion   | 3.577708764 |
| positive regulation of secretion by cell                                     | 3.299831646 |
| protein secretion  | 4.146139914 |
| regulation of peptide secretion  | 3.771236166 |
| regulation of protein secretion  | 3.771236166 |
| regulation of tumor necrosis factor production                               | 3.31662479  |
| tumor necrosis factor production   | 3.464101615 |
| Chemotaxis   |             |
| Terms  | Z-score     |
| cell chemotaxis  | 3.872983346 |
| chemotaxis   | 4.358898944 |
| leukocyte chemotaxis   | 3.31662479  |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| macrophage chemotaxis  | 2.236067977 |
| monocyte chemotaxis  | 2           |
| positive regulation of chemotaxis                              | 2.828427125 |
| regulation of chemotaxis                                       | 3.16227766  |
| ameboidal-type cell migration                                  | 3.050851079 |
| blood vessel endothelial cell migration                        | 2.449489743 |
| endothelial cell migration                                     | 2.121320344 |
| epithelial cell migration                                      | 2.529822128 |
| epithelium migration   | 2.529822128 |
| leukocyte migration  | 3.605551275 |
| macrophage migration   | 2.449489743 |
| mononuclear cell migration                                     | 2.449489743 |
| myeloid leukocyte migration                                    | 3           |
| positive regulation of blood vessel endothelial cell migration | 2.236067977 |
| positive regulation of cell migration                          | 5.112077203 |
| positive regulation of epithelial cell migration               | 2.121320344 |
| positive regulation of leukocyte migration                     | 2.645751311 |
| regulation of blood vessel endothelial cell migration          | 2.449489743 |
| regulation of endothelial cell migration                       | 2.121320344 |
| regulation of epithelial cell migration                        | 2.529822128 |
| regulation of leukocyte migration                              | 2.828427125 |
| regulation of macrophage migration                             | 2           |
| regulation of mononuclear cell migration                       | 2           |
| tissue migration   | 2.529822128 |
| positive regulation of locomotion                              | 5.112077203 |
| positive regulation of cell motility                           | 5.112077203 |
| taxis  | 4.472135955 |
| maintenance of location  | 3.356585567 |
| positive regulation of cellular component movement             | 5.112077203 |
| Immunity and inflammation                                      |             |
| Terms  | Z-score     |
| leukocyte activation involved in immune response               | 3           |
| leukocyte degranulation  | 2.236067977 |
| leukocyte mediated immunity                                    | 3.605551275 |
| leukocyte proliferation  | 3.16227766  |
| macrophage activation  | 2.236067977 |
| mast cell activation   | 2.449489743 |
| mast cell activation involved in immune response               | 2           |
| mast cell degranulation  | 2           |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| mast cell mediated immunity                                | 2           |
| mononuclear cell proliferation                             | 3.16227766  |
| myeloid cell activation involved in immune response        | 2.449489743 |
| myeloid leukocyte activation                               | 3.605551275 |
| myeloid leukocyte mediated immunity                        | 2.449489743 |
| negative regulation of cell activation                     | 3.050851079 |
| negative regulation of immune system process               | 3.900067476 |
| negative regulation of leukocyte activation                | 3.16227766  |
| negative regulation of lymphocyte activation               | 2.645751311 |
| cell activation involved in immune response                | 3           |
| inflammatory response                                      | 4.041451884 |
| neuroinflammatory response                                 | 2           |
| positive regulation of defense response                    | 2.886751346 |
| regulation of defense response                             | 3.130495168 |
| regulation of leukocyte activation                         | 3.638034376 |
| regulation of mast cell activation                         | 2           |
| T cell activation  | 2.840187787 |
| regulation of cell activation                              | 3.709704134 |
| Ion transport and homeostasis                              |             |
| Terms  | Z-score     |
| calcium ion homeostasis                                    | 3           |
| cation homeostasis   | 4.642383454 |
| cellular calcium ion homeostasis                           | 3           |
| cellular cation homeostasis                                | 4.535573676 |
| cellular divalent inorganic cation homeostasis             | 3.299831646 |
| cellular ion homeostasis                                   | 4.535573676 |
| cellular iron ion homeostasis                              | 2.645751311 |
| cellular metal ion homeostasis                             | 4.314554973 |
| cellular transition metal ion homeostasis                  | 3.16227766  |
| divalent inorganic cation homeostasis                      | 3.299831646 |
| inorganic ion homeostasis                                  | 4.642383454 |
| iron ion homeostasis                                       | 2.828427125 |
| metal ion homeostasis                                      | 4.426352064 |
| transition metal ion homeostasis                           | 3.31662479  |
| transition metal ion transport                             | 2.449489743 |
| regulation of cytosolic calcium ion concentration          | 2.713602101 |
| positive regulation of cytosolic calcium ion concentration | 2.529822128 |
| Lysosome   |             |
| Terms  | Z-score     |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| lysosomal membrane                                   | 2.828427125 |
| lysosome   | 4.426352064 |
| lysosome localization                                | 2.236067977 |
| lytic vacuole  | 4.426352064 |
| lytic vacuole membrane                               | 2.828427125 |
| late endosome  | 3.050851079 |
| late endosome membrane                               | 2           |
| endosomal part                                       | 3           |
| endosome membrane                                    | 3           |
| vacuolar membrane                                    | 3.31662479  |
| vacuolar part  | 3.31662479  |
| vacuole  | 4.642383454 |
| cytoplasmic vesicle part                             | 3.050851079 |
| Cellular response to stimulus                        |             |
| Terms  | Z-score     |
| cellular response to inorganic substance             | 2.496150883 |
| cellular response to metal ion                       | 2.496150883 |
| response to inorganic substance                      | 3.837612894 |
| response to metal ion                                | 3           |
| response to wounding                                 | 4.314554973 |
| negative regulation of response to external stimulus | 2.496150883 |
| positive regulation of response to external stimulus | 3.356585567 |
| regulation of response to external stimulus          | 4.157609203 |
| regulation of response to wounding                   | 2.333333333 |
| Angiogenesis   |             |
| Terms  | Z-score     |
| angiogenesis   | 3.299831646 |
| blood vessel development                             | 2.558408596 |
| blood vessel morphogenesis                           | 2.836832573 |
| positive regulation of vasculature development       | 3.31662479  |
| positive regulation of angiogenesis                  | 3.31662479  |
| vasculature development                              | 2.710687383 |
| regulation of vasculature development                | 2.496150883 |
| regulation of angiogenesis                           | 2.496150883 |
| cardiovascular system development                    | 2.710687383 |
| Cell survival  |             |
| Terms  | Z-score     |
| negative regulation of neuron apoptotic process      | 2.121320344 |
| neuron apoptotic process                             | 3.050851079 |

## SUPPLEMENTARY DATA

|  |             |
|--|-------------|
| regulation of neuron apoptotic process           | 2.713602101 |
| negative regulation of neuron death              | 3.050851079 |
| neuron death                                     | 3.577708764 |
| regulation of neuron death                       | 3.152963125 |
| Protein-lipid complex                            |             |
| Terms  | Z-score     |
| plasma lipoprotein particle                      | 2           |
| plasma lipoprotein particle organization         | 2           |
| protein-lipid complex                            | 2           |
| protein-lipid complex subunit organization       | 2           |
| lipoprotein particle                             | 2           |
| regulation of plasma lipoprotein particle levels | 2.236067977 |

**Supplementary Table 5.** Statistics reporting.

| Fig No. | Description               | Group (n)   | Test used   | Degree of freedom and P value  |
|---------|---------------------------|---|---|--|
| Fig1b   | Iba1+ cell body volume    | Cortex: young(98) aged(89);<br>Striatum: young(103) aged(102);<br>SVZ: young(53) aged(82);<br>Hippocampus: young(65) aged(96)     | Cortex: Unpaired t-test, two tailed;<br>Striatum: Unpaired t-test, two tailed;<br>SVZ: Unpaired t-test, two tailed;<br>Hippocampus: Mann Whitney test | Cortex: t (185)=-9.079,***p<0.001;<br>Striatum: t (161.683)=-9.542,***p<0.001;<br>SVZ: t(133)=-3.893,***p<0.001<br>Hippocampus: ***p<0.001;                        |
| Fig1c   | Iba1+ cell number         | Young (23): cortex (5), striatum (6), Hippocampus (6), SVZ (6);<br>Aged (24): cortex (6), striatum (6), Hippocampus (6), SVZ (6); | Mann Whitney test   | *p=0.042   |
| Fig2d   | Proportion of subclusters | Young (8) aged (8)  | Unpaired t-test, two tailed   | C0:t(14)=1.321,p=0.208;<br>C1:t(14)=0.531,p=0.604<br>C2:t(14)=-1.244,p=0.234<br>C3:t(14)=-4.511,***p<0.001<br>C4:t(14)=2.734,*p=0.016<br>C5:t(14)=-3.361,**p=0.005 |
| Fig2e   | Markers of C0             | C0 (1922) others (1931)   | Wilcoxon rank sum test, Bonferroni correction   | ***p<0.001   |