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Master Thesis

Unraveling the microglia-oligodendrocyte transcriptomic crosstalk for the identification of myelination biomarkers

by

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Abstract

Background: While there is information on transcriptomic biomarkers of demyelination, the heterogeneity in the methods and cell types/tissues used makes it difficult to select transcriptomic biomarkers for demyelination studies. In addition, there is scarce data on the crosstalk between microglia and oligodendrocyte progenitor cells (OPCs), 2 of the 4 cell types involved in demyelination/remyelination processes.

Objectives: To identify 1) transcriptomic biomarkers of demyelination in microglia, OPCs and *corpus callosum* following a similar pipeline, and 2) microglia ligands and OPC receptors and targets genes involved in the microglia-OPC crosstalk.

Methods: Data were obtained from all available studies of gene expression data by microarray in mice samples treated with cuprizone available at GEO/Array Express. Differential expression analyses were performed to identify transcriptomic biomarkers. The following pipeline was used: quality control, normalization, annotation, gene filtering, aggregation, batch effect correction, differential expression analysis, annotation, plotting and functional analysis. The crosstalk analysis was performed with the NicheNet model for intercellular communication using expressed genes in microglia and OPCs obtained from the differential expression analysis. Ligand-target regulatory potentials, ligand-receptor networks and ligand-receptor interactions were obtained from the NicheNet model. Analyses were performed in R.

Results: There were 166, 12, and 2730 differential expressed genes (DEGs) identified in the *corpus callosum*, microglia and OPC differential expression analyses, respectively. DEGs included genes associated with demyelination such as Ninj2, Lpl, and Mobp. DEGs identified in the *corpus callosum* and OPC analyses were associated with GO terms and Wikipathways related to myelin. There was 1 DEG identified in both the microglia and the OPCs analyses, and 95 DEGs identified in both the *corpus callosum* and OPCs analyses. We identified 45 potential ligands of microglia that could affect gene expression in OPCs, 115 DEGs in OPCs that were predicted target genes of these ligands, and 43 potential OPC receptors of the identified microglia ligands. Some of the identified microglia ligands, and OPC receptors and targets genes, were differentially expressed in cuprizone treated samples compared to control and were associated with demyelination and myelin formation.

Conclusions: The differential expression pipeline was able to identify transcriptomic biomarkers associated to demyelination in studies using different platforms and cell types/tissues. The crosstalk analysis between microglia and OPCs identified novel microglia ligands, and OPC receptors and target genes.

Table of contents

1. Introduction

Myelin is a modified plasma membrane that covers nerve axons to allow the correct transmission of electrical impulses and protect nerves. Myelin has a high proportion of lipids (70-85%) and a low proportion of proteins (15-30%). The main lipids and proteins in myelin are galactosylceramide, ethanolamine-containing plasmalogens, cholesterol, proteolipid protein, myelin basic protein, and 2':3'-Cyclic nucleotide-3'-phosphodiesterase among others [1, 2].

In the central nervous system, myelin is produced by oligodendrocytes. Oligodendrocytes are continuously developed in the healthy adult brain, and myelin is produced and remodeled during the whole life [3]. Oligodendrocytes originate from oligodendrocyte precursor cells (OPCs), which can proliferate, migrate and differentiate into myelinating oligodendrocytes [4]. Oligodendrocyte differentiation into a myelinating cell is regulated by several cell types including microglia, OPCs and astrocytes. Microglia are immune cells of the central nervous system, and their functions include to remove cells, pathogens, and myelin debris among others [5]. Microglia can stimulate the survival, migration and differentiation of OPCs. However, activated microglia can also have detrimental effects on OPCs [6]. Astrocytes can be inactive or active, they promote synapse and blood barrier functions, glial scar formation, and have an effect on myelination. Regarding the latter, astrocytes promote OPC proliferation and differentiation, and myelin production and maintenance [7]. However, astrocytes can also inhibit oligodendrocyte differentiation directly and by activating the microglia, depending on the surrounding microenvironment [8].

Demyelination is the process that results from the loss of myelin and lack of subsequent myelin production (remyelination). This process occurs in several diseases such as multiple sclerosis. In demyelinating disorders, oligodendrocytes die and differentiation of OPCs to mature myelin-forming oligodendrocytes is affected.

Demyelination can be studied using human samples and *in vitro* and *in vivo* models. *In vitro* models include cultures of immortalized cell lines obtained from mammalian brain cells and slice cultures. These models have limitations such as the difficulty of extrapolating cell line results to tissues and the technical issues of slice culture obtaining [9]. *In vivo* models can be classified in autoimmune, viral, chemical, and transgenic models. Autoimmune models include animal models of diseases that show demyelination among others. The most used autoimmune disease model is experimental allergic encephalitis (EAE), which is induced by autoantigen and Freund's adjuvant administration or transfer of autoreactive T cells [10, 11]. In viral models, demyelination is induced after infection with theiler's murine encephalomyelitis virus, A7 strain of Semliki Forest virus,

herpesvirus causing japanese macaque encephalomyelitis, and mouse hepatitis virus causing panencephalitis [10-13]. Viral models but not EAE models induce microglial activation [10]. Chemical models are those in which cuprizone, lysolecithin, or ethidium bromide are given to the animals. Cuprizone and lysolecithin cause extensive chronic demyelination while the treatment is maintained and remyelination afterwards [9]. However, remyelination after lysolecithin treatment depends on several factors. Cuprizone is a copper chelator that induces oligodendrocyte apoptosis, which causes demyelination and activation of astrocytes and microglia. Regarding ethidium bromide treatment, demyelination is due to astrocyte dysfunction [14]. Transgenic models have been developed by introducing mutations in myelin proteins [15]. Zebrafish transgenic lines of fluorescent oligondendrocytes and OPCs can also be used to study remyelination. EAE and cuprizone are the most commonly used models to study multiple sclerosis and demyelination [16].

Due to the severity of demyelinating diseases it is essential to have clear biomarkers to study disease mechanisms and potential treatments. However, even in the most common demyelination models the techniques used, cell types/brain regions analyzed, and biomarkers assayed are heterogeneous [17-20]. This heterogeneity makes it difficult to prioritize biomarkers in subsequent studies. Among the different types of biomarkers available, including omic ones, transcriptomic approaches make it possible to identify new mechanisms of disease and to analyze most/all of the genes expressed after a specific treatment. Non-omic biomarkers allow only the study of already known genes/proteins, depend much on the primers/antibodies/experiment selected, and their analysis is time-consuming [21]. Genomic biomarkers give information of the DNA sequence associated to a disease rather than on the effect after a treatment. Proteomic/metabolomic studies can only analyze a subset of the proteome/metabolome due to its heterogeneity and need of different techniques. And epigenomics gives information of gene expression regulators (methylation, histone modifications, microRNAs…) but not on the effect on gene expression which are more downstream and closer to the disease phenotype.

The microglia-astrocyte-oligodendrocyte crosstalk is key in OPCs differentiation to myelin-forming oligodendrocytes, and thus, its study is central to find new mechanisms in demyelinating diseases [3]. While some information is available for this crosstalk, there is scarce data on the relationship between microglia and OPCs. Moreover, the ligands, receptors, and target genes involved in the crosstalk between microglia and OPCs after cuprizone treatment are unknown.

2. Goals

The objectives of this Final Master Project were:

1. To identify transcriptomic demyelinating biomarkers in different cell types/regions due to cuprizone treatment following a similar pipeline
    a. To identify the differentially expressed genes (DEGs) in *corpus callosum* samples from cuprizone treated and control mice
    b. To identify the DEGs in microglia samples from cuprizone treated and control mice
    c. To identify the DEGs in OPC samples from cuprizone treated and control mice
2. To identify the microglia ligands, and the OPC target genes and receptors involved in the transcriptomic crosstalk between microglia and OPCs during cuprizone treatment in mice

3. Methods

3.1. Data

Transcriptomic data was obtained from GEO with the GEOquery package [22]. We searched GEO/ArrayExpress on the 1st of February 2021 to identify studies which had analyzed gene expression by microarray in mice treated or not with cuprizone. This search yielded 5 studies, all of which were available in GEO (Table 3.1).

3.2. Software

All analyses were done in R version 4.0.4 [23], using RStudio version 1.1.463, and a ThinkPad Yoga 460 computer with an Intel® Core™ i7-6500U CPU @ 2.50GHz with 8,00 GB RAM. Operating system was Windows 10 Pro version 20H2.

3.3. Study design

In objective 1, our goal was to run the most similar analysis possible in microglia, OPCs, and *corpus callosum,* and select a small number of demyelination biomarkers to be used in subsequent experiments. To do so, we did a differential gene expression analysis of the 2 microglia studies together, as they used the same platform, of the OPC study, and of the study of *corpus callosum* GSE100663. We did not use the study of *corpus callosum* GSE70475 because

there was no group without cuprizone treatment which was one of our analysis groups.

In objective 2, our goal was to identify the ligands of microglia and the receptors and target genes of OPCs involved in the crosstalk between these 2 cell types after cuprizone treatment. To do so, we applied a published method to model intercellular communication using differential expressed genes and group data of the 2 microglia studies and of the OPCs study [24].

3.4. Differential gene expression analysis

3.4.1. Preprocessing (Figure 3.1)

Agilent studies were hybridized in one color arrays, and images were read with Agilent (GSE100663) or Genepix (GSE48872) software using the limma package [25]. Column information on flags, control type and expression level was extracted. Spot quality weights were extracted with the wt.function argument. Specifically, 0.1 weight was given to spots with negative flags. Quality control was performed with the oligo [26], limma and affy [27] packages, and included boxplots and density plots (histograms) of log-intensities, and MAplots. In Affymeytrix studies (GSE84113, GSE66926), quality control included also image inspection and plots of relative log expression values (RLE) and of normalized unscaled standard errors (NUSE).

In Affymetrix studies, background correction, normalization and summarization was done with the rma function, which performs quantile normalization, and summarization with the median-polish method. After binding expression data of the 2 microglia studies, quantile normalization (casper package [28]) on the whole set of samples was performed. In agilent studies, background correction was performed using convolution of normal and exponential distributions, quantile normalization was applied, and summarization was done by replacing array replicates with their average. In the corpus callosum study (Agilent), the normalization was performed as for Agilent studies. In addition, the normalization described in the published article was examined but not used, in order to use a validated and similar strategy between studies. The published normalization was to divide the expression by the 75th percentile of the signal for each array. After preprocessing, normalized data was examined using boxplots.

3.4.2. Annotation, gene filtering, aggregation and batch effect (Figure 3.2)

mogene10sttranscriptcluster.db and mgug4122a.db were used to annotate Affymetrix and Agilent studies, respectively, with the AnnotationDbi package. Gene filtering in all studies included exclusion of probes with no symbol and exclusion of probes with low expression. Gene filtering for low expression was defined as within the 30th percentile of lower intensity medians in at least the smallest experimental group. This common strategy for all studies was preferred

over the limma strategy of filtering with a cutoff in the gIsWellAboveBG column to keep probes that are expressed above the background, because this strategy was only valid for some Agilent arrays. Agilent studies included also gene filtering for control and negative flagged probes as this information was available. Sample clustering (aggregation) was performed to examine how samples clustered together by treatment group, scan date, and experiment. Aggregation by treatment was performed in the 3 analyses using hierarchical clustering and principal component analysis (stats, graphics, and scatterplot3d [29] packages). Aggregation by scan date was done in the *corpus callosum* and OPC analyses only as in the microglia analysis, one study had 2 samples and the other read all samples within 1 hour. Aggregation by experiment was done in the in microglia analysis as it was the only analysis with more than 1 study. In the hierarchical clustering, distances were based on correlations and the linkage method was Ward's clustering criterion, which squares dissimilarities before cluster updating. Experiment effect was corrected in the microglia analysis with the ComBat method (sva package) using a parametric empirical Bayes framework, while preserving the treatment condition.

3.4.3. Differential expression, annotation and functional analysis (Figure 3.3)

We fitted generalized linear models to explain the observed expression by treatment. We compared cuprizone treated vs control samples. Moderated t-statistics were computed by allowing an intensity-trend for the prior variance (all analyses) and/or robustifying for outlier sample variances (in OPC and in *corpus callosum* analysis) if needed. These conditions were included if non-constant residual standard deviation or outliers were identified in the plots of residual standard deviation vs average log expression of the fitted linear models (Supplementary Figure 3.1). p-values were adjusted for multiple comparison using the Benjamini-Hochberg method [30] to control for false discovery rate (FDR). Duplicated assigned genes were removed by grouping them by name and selecting the one with the lowest p-value. Volcano plots were created with the base package by plotting log fold changes and the –log10 transformation of adjusted p-values. Heatmaps with all significant DEGs or with the top 10 (*corpus callosum* and OPC analysis) were done to examine the ability of the DEGs to separate treatment groups. In the *corpus callosum* analysis we did an extra analysis, using the GEO2R utility, comparing 4 weeks cuprizone treated and control samples with correction for FDR, because contrary to the published article no DEGs were identified in the analysis. DEGs were presented in html tables (htmltools package).

Functional analysis included an over-representation analysis of Gene Ontology (GO) molecular-level functions and an over-representation analysis of WikiPathways (clusterProfiler package [31]) using the identified DEGs. p-values were obtained with the hypergeometric test. We chose WikiPathways in addition to the classic GO because it is continuously updated and curated and because it includes other pathways initiatives such as Reactome. p-values were

adjusted for multiple comparisons with the Benjamini-Hochberg method. The 20 most significant molecular functions and the significant pathways were represented using dotplots (TimeSeriesExperiment and enrichplot packages). Due to the large number of DEGs in the OPC analysis, functional analysis was done with the DEGs with an adjusted p-value < 0.001 (n=359).

Number of common DEGs between the 3 analyses were presented with a venn diagram plot (VennDiagram package). A functional analysis was performed with the common DEGs as described above.

3.5. Microglia and OPC crosstalk

The crosstalk analysis was performed with the NicheNet model for intercellular communication [24]. NicheNet allows the analysis of sender cell ligands on receiver cell expression using expression data of interacting cells. This method makes it possible to identify interactions between sender cell ligands and receiver cell receptors, as well as the effect of these interactions on target gene expression in the receiver cells. The NicheNet model has been successfully used to unravel intercellular communications in the embryonic kidney [32] and novel interactions in the immune microenvironment of ovarian cancer [33].

We applied the NicheNet model using the nichenetr package from R. To do this analysis we needed to define: a ligand-target model with the potential that a particular ligand might regulate the expression of a specific target gene, expressed genes in the sender cells (microglia), expressed genes in the receiver cells (OPCs), a gene set of interest in OPCs the expression of which could be affected by other cell types, and background of genes expressed by OPCs.

The ligand-target model used was the one developed by NicheNet as a ligand-target matrix. This matrix was obtained from Zenodo (https://zenodo.org/record/3260758/files/ligand_target_matrix.rds). The expressed genes in microglia and OPCs was the expression data after normalization, annotation, and filtering by control, negative, and with no symbol probes obtained in the microglia and OPC DEG analyses. The expressed genes in microglia and OPCs were further filtered as genes which expression was over the 60% or the 75% percentile of the median gene expression, respectively. This was done not to include low expressed genes and to follow NicheNet protocol suggesting that expressed genes were between 5000-10000 (expressed genes in microglia: 9942, expressed genes in OPCs: 10523). The gene set of interest was defined as the OPCs DEGs with a p-value <0.01. The background of genes were all genes expressed by OPCs except for the gene set of interest.

As potential ligands we used those expressed by microglia that can bind a putative receptor in OPCs. As potential receptors we used those expressed by OPCs that can bind a putative ligand from microglia. Putative ligands and receptors were gathered from a NicheNet ligand-receptor network in Zenodo

(https://zenodo.org/record/3260758/files/lr_network.rds) restricted to those described in curated databases.

Ligand activity was assessed by examining how well the ligands predicted the observed changes in gene expression in the gene set of interest compared to the background genes using the Nichenet ligand-target matrix with regulatory potential scores. Ligand activity was ranked according to the Pearson correlation coefficient. We examined the regulatory potential scores for interactions between the identified ligands and OPC targets by analyzing genes that were differentially expressed in OPCs and belonged to the 100 most strongly predicted targets of at least one of the top ranked ligands. We identified the OPC receptors that could bind to microglia ligands by using the potential receptors and weights of ligand-receptor interactions (https://zenodo.org/record/3260758/files/weighted_networks.rds). Ligands and receptors were ordered with hierarchical clustering using the Ward's clustering criterion. Association between microglia ligands and OPC receptors and targets was visualized with heatmaps. We included expression data of ligands, targets, and receptors from the microglia and the OPC DEG analyses to analyze differences in expression between cuprizone samples and controls. Differences in expression were analyzed with t-tests and adjusted for multiple comparisons using the benjamini-hochberg method. Tables of differentially expressed ligands, targets and receptors were created including mean group expression, adjusted p-values, fold change (ratio of mean expression in cuprizone samples/control) and annotation. Annotation of gene names was done with the mapIds function and the org.Mm.eg.db package.

4. Results and discussion

4.1. Differential gene expression analysis

The quality control showed that data from the 4 included studies had sufficient quality to be analyzed. After normalization, log-intensity boxplots and density distributions were very similar among samples (Supplementary Figure 4.1). Gene filtering reduced the number of probes as depicted in Supplementary Table 4.1.

In the *corpus callosum* study, there was certain aggregation by treatment and no aggregation by scan date. While 4 samples aggregated as expected, 3 did not (1 control, 2 treated with cuprizone for 4 weeks) (Figure 4.1A). We performed the analysis with all samples and we obtained no DEGs, contrary to the published study [20] but in line with the GEO2R analysis, suggesting that normalization and/or gene expression were analyzed using non-standard methods or that some samples were excluded. We explored the normalization strategy described in Martin NA et al. [20], different normalization and summarization options, but no DEGs were identified. Taking into account the

observed differences in aggregation we excluded the 2 most different samples based on aggregation (1 control and 1 cuprizone treated sample) and proceed with the analysis with the remaining 5 samples: 2 control and 3 cuprizone treated samples, which aggregation is shown in Figure 4.1B. In the microglia analysis, samples aggregated by experiment and by treatment within each experiment except for one cuprizone sample (Figure 4.1C). Aggregation by experiment was corrected after adjusting the data for experiment effect (Figure 4.1C). In the OPC analysis, there was aggregation by treatment and no aggregation by scan date (Figure 4.1D).

In the *corpus callosum* analysis, we identified 166 DEGs, 80 downregulated and 86 upregulated (Figures 4.2-3, Table 4.1). The 10 most DEGs included Ninj2, which promotes neurite outgrowth and is involved in myelination networks [34]. Ninj2 was upregulated in cuprizone treated samples, which could indicate that demyelination may trigger signals to restore the myelin in *corpus callosum*. *Corpus callosum* samples from mice treated with cuprizone and from control mice were clearly separated using all DEGs and using the 10 most DEGs (Figure 4.3). There were 6 significant molecular functions associated with the identified DEGs, including structural constituent of myelin sheath (Figure 4.4). There were also 115 associated biological processes, several of which were related to myelin (cholesterol biosynthesis, myelination, axon ensheathment, oligodendrocyte differentiation, etc). The significant Wikipathways associated with the DEGs included cholesterol biosynthesis and cholesterol metabolism (Figure 4.5), which are key pathway in myelination [35].

There were 12 DEGs in microglia samples treated with cuprizone compared to control, all upregulated (Figures 4.6A-4.7A, Table 4.2). Of those, lipoprotein lipase [36] and low density lipoprotein receptor [37] have been previously associated with myelinization. There was 1 molecular function associated with the identified DEGs (carbohydrate binding), 23 biological processes (not clearly related to myelin) and no WikiPathways.

In the OPC analysis, we identified 2730 DEGs. Of those, 1372 were downregulated, and 1358 were upregulated in the cuprizone teated samples compared to control (Figure 4.6B, 4.7B-C, Table 4.3). OPC samples from mice treated with cuprizone and from control mice were clearly separated using all DEGs and also using the 10 most DEGs (Figure 4.7 B-C). Among the DEGs, there were genes associated with demyelination such as Mobp and Mog genes, which were downregulated in cuprizone treated OPCs [19]. The most significant DEGs (adjusted p-value <0.001) were associated with 19 molecular functions and 226 biological processes, including regulation of axon extension, neurogenesis, and neuron projection development among others. There were 6 significant WikiPathways as shown in Figure 4.8, which included cholesterol and sphingolipid metabolism. Cholesterol and sphingolipids are major components of myelin and their altered metabolism is associated with neurological and neurodegenerative diseases [38].

There were no DEGs identified in the 3 tissues/cell types. There was 1 DEG identified in the microglia and in the OPC analyses (Lgals3), and 95 DEGs identified in the *corpus callosum* and in the OPC analyses (Figure 4.9 and Table 4.4). Lgals3 fosters oligodendrocyte differentiation, which contributes to myelin integrity and function [39]. The 95 common DEGs in *corpus callosum* and OPC samples included several genes that encoded myelin related proteins such as: Mog, Opalin, Mbp and Omg. These 95 DEGs were associated with 4 molecular functions and 86 biological processes such as cholesterol biosynthesis, myelination, axon ensheathment and oligodendrocyte differentiation among others. The 95 DEGs were also associated with 4 pathways including spinal cord injury and adipogenesis genes (Figure 4.10). Spinal cord injury is frequently associated with demyelination [40]. We expected a larger number of genes differentially expressed between cuprizone treated and control samples shared by the three cell types/tissues. Many factors can contribute to this low number of common DEGs between cell types/tissues. On the one hand, the number of DEGs identified in microglia samples is very small, this could be the result of combining two different studies with a large heterogeneity within cuprizone treated and control samples. Similarly, the number of DEGs identified in *corpus callosum* samples is also small, and could be also due to sample heterogeneity. On the other hand, microglia and OPC samples could contain other cell types, and *corpus callosum* samples could contain more oligodendrocytes/OPCs than microglia o other cell types. In addition, basal gene expression patterns and gene expression after cuprizone treatment are probably very different in these cell types/tissues.

4.2. Microglia and OPC crosstalk

We identified 47 potential ligands in microglia that could affect the expression of the gene set of interest in OPCs after cuprizone treatment (Table 4.5). All ligands had a similar potential to regulate the gene set of interest. All potential ligands had active target links with OPC genes differentially expressed after cuprizone treatment. We identified 115 DEGs in OPCs that were predicted targets of the identified ligands (Figure 4.11). Analysis of ligand-receptor interaction yielded 43 potential receptors of identified ligands expressed by OPCs after cuprizone treatment (Figure 4.12). The maximum interaction potential was found for the following ligand-receptor pairs: CSF1-CSFR, GAS6-AXL/TYRO3, IGF1-IGF1R, JAM2-JAM3, PTPRC-CD22, APOE-VLDLR, LRPAP1-VLDLR, SMAD4D-PLXNB1.

Expression of microglia ligands in microglia samples is presented in Figure 4.13. We found that Spp1 (Secreted Phosphoprotein 1) and Plau (Plasminogen Activator, Urokinase) ligands had borderline significant differences in their expression between treatment groups (Table 4.6). The expression of both ligands was higher in microglia from cuprizone treated mice compared to control. This result is in line with a previous study showing that Spp1 (or osteopontin) is upregulated during *in vivo* demyelination and enhances myelin

formation [41]. In addition, tissue plasminogen activator promotes axonal outgrowth on central nervous system myelin after injury [42]. Among the 115 identified OPC targets, 107 were differentially expressed between OPCs from cuprizone treated and from control mice (Table 4.7). Expression of OPC target genes from microglia ligands in OPC samples is shown in Figure 4.14. The most differentially expressed targets were Bbc3, Gadd45b and Hist1h3d. Bbc3 has been associated with programmed cell death of premyelinating oligodendrocytes [43]. Bbc3 was upregulated in OPCs from cuprizone treated mice compared to control what could indicate cell death promotion in OPCs after cuprizone treatment. Of the 43 receptors, 15 were differentially expressed between OPCs from cuprizone treated and control mice (Table 4.8). Expression of OPC receptors from microglia ligands in OPC samples is presented in Figure 4.15. The most differentially expressed was Jam3. Members of the Jam family, such as Jam-c, alter the integrity of the myelin sheath when are not present [44]. Jam3 was downregulated in OPCs from cuprizone treated compared to control mice, which could contribute to the loss of myelin integrity that occurs in cuprizone induced demyelination.

5. Limitations

Our study has some limitations. First, the number of samples in the available studies was small and this could affect the number of DEGs after cuprizone treatment, the common DEGs between cell types and tissues, and the cross-talk analysis. However, taking into account that most of the identified DEGs, ligands, targets and receptors were associated with myelination processes we believe that our study yielded robust results. Second, microglia and OPC samples could include other cell populations, and it is not known which cell types are present in the *corpus callosum* samples. Although this limitation could be analyzed using deconvolution methods, the small sample size of the included studies and the heterogeneity and lack of validation of deconvolution methods prompt us not to include this analysis in the present study. However, we will explore deconvolution methods in subsequent analyses. Third, we analyzed separately the 3 cell types/tissues as gene expression was measured using different arrays and software. Another option could be to perform the analysis with all samples, regardless of the cell type/tissue of origin. If all samples were analyzed at the same time we could use quantile normalization and batch effect adjustment such as in the microglia analysis. We did not use this strategy because our goals were 1) to identify DEGs by cell type/tissue, and 2) to define microglia and OPC expression pattern after cuprizone treatment to analyze the crosstalk between these cell types. In addition, the analysis of all samples would have much heterogeneity, as we are including few patient samples, which are much more heterogeneous than cell lines. Finally, it would be useful to validate experimentally the most DEGs, for example by qPCR. To

tackle this limitation we will perform validation experiments in the following months.

6. Conclusions

We developed a similar strategy to select biomarkers of demyelination after cuprizone treatment in different cell types/tissues from mice. The identified biomarkers were associated with GO molecular functions and biological processes, and with Wikipathways associated with myelination. In addition, some of these biomarkers had been previously associated with demyelination. These biomarkers could thus be used in subsequent experiments to evaluate demyelination in cuprizone treated mice and this strategy could be applied to other cell types and demyelination treatments. We also performed an *in silico* analysis to identify ligands, receptors, and target genes involved in the crosstalk between microglia and OPCs. Some of the ligands, receptors, and target genes identified were associated with demyelination and were differentially expressed in samples from cuprizone treated compared to control mice. This result suggests that crosstalk analysis, at least in cuprizone induced demyelination, can be studied using data from different experiments. We found novel demyelination biomarkers as well as novel ligands, receptors and target genes in the crosstalk between microglia and OPCs, which warrants further validation studies.

7. Appendices

7.1. Tables

Table 3.1. Studies with gene expression analysis by microarray of control and cuprizone treated brain samples/cells.

GEO Study	Platform	Cell type/brain region	Length of cuprizone	Number of samples in	Number of samples in

			treatment	control group	treatment group
GSE100663	Agilent whole mouse 4x44k	*Corpus callosum*	2/4 weeks	3	3 (2 weeks)/4 (4 weeks)
GSE70475	Affymetrix Mouse Gene 1.0 ST	*Corpus callosum*	6/12 weeks	0	4/5
GSE84113	Affymetrix Mouse Gene 1.0 ST	Microglia	4 weeks	2	3
GSE66926	Affymetrix Mouse Gene 1.0 ST	Microglia	4 weeks	1	1
GSE48872	Agilent whole mouse 4x44k	OPCs	5 weeks	3	4

OPCs: Oligodendrocyte progenitor cells

Table 4.1. DEGs identified in the *corpus callosum* of mice treated with cuprizone for 4 weeks compared to *corpus callosum* from control mice.

Probe ID	Symbol	Gene name	Log2 fold change	p-value	Adjusted p-value
A_52_P532982	Gdf15	growth differentiation factor 15	-3.86	3.37e-07	8.51e-03
A_51_P285669	Pigz	phosphatidylinositol glycan anchor biosynthesis, class Z	2.54	1.35e-06	1.10e-02
A_51_P331570	Trib3	tribbles pseudokinase 3	-4.40	1.77e-06	1.10e-02
A_51_P329975	Ninj2	ninjurin 2	1.92	2.01e-06	1.10e-02
A_51_P161612	Ccng1	cyclin G1	-1.93	2.41e-06	1.10e-02
A_51_P230734	Slc34a3	solute carrier family 34 (sodium phosphate), member 3	1.76	2.78e-06	1.10e-02
A_51_P269216	Atf5	activating transcription factor 5	-3.41	3.05e-06	1.10e-02
A_51_P197043	Xrcc3	X-ray repair complementing defective repair in Chinese hamster cells 3	1.91	4.10e-06	1.29e-02
A_52_P533146	Ddit3	DNA-damage inducible transcript 3	-1.70	5.40e-06	1.51e-02
A_51_P493987	Moxd1	monooxygenase, DBH-like 1	-2.59	7.51e-06	1.60e-02
A_52_P207163	Eda2r	ectodysplasin A2 receptor	-1.12	7.61e-06	1.60e-02
A_52_P395149	Smtnl2	smoothelin-like 2	1.65	8.68e-06	1.69e-02
A_51_P432460	Ppp1r14a	protein phosphatase 1, regulatory inhibitor subunit 14A	3.67	9.42e-06	1.70e-02
A_52_P154710	Sesn2	sestrin 2	-2.20	1.05e-05	1.74e-02
A_51_P363947	Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)	-3.72	1.13e-05	1.74e-02
A_51_P219918	Tmem125	transmembrane protein 125	3.46	1.21e-05	1.74e-02
A_51_P479230	Nat8	N-acetyltransferase 8 (GCN5-related)	-1.57	1.24e-05	1.74e-02
A_51_P516741	Tmprss5	transmembrane protease, serine 5 (spinesin)	1.65	1.34e-05	1.74e-02
A_51_P273639	Slc7a5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	-1.73	1.38e-05	1.74e-02
A_52_P329207	Wfdc18	WAP four-disulfide core domain 18	1.87	1.47e-05	1.77e-02
A_51_P129502	Slc7a11	solute carrier family 7 (cationic amino acid transporter, y+ system), member 11	-2.37	1.75e-05	1.87e-02
A_51_P283473	Fibin	fin bud initiation factor homolog (zebrafish)	-1.70	1.82e-05	1.87e-02
A_51_P213544	Klf4	Kruppel-like factor 4 (gut)	-1.71	1.84e-05	1.87e-02
A_51_P330428	Eif4ebp1	eukaryotic translation initiation factor 4E binding protein 1	-2.33	1.85e-05	1.87e-02

A_51_P472901	Slc3a2	solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2	-1.54	1.94e-05	1.89e-02
A_51_P241407	Arap2	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 2	-1.39	2.08e-05	1.95e-02
A_51_P337925	Gzmm	granzyme M (lymphocyte met-ase 1)	-1.60	2.20e-05	1.98e-02
A_51_P384230	Sgk2	serum/glucocorticoid regulated kinase 2	2.93	2.78e-05	2.35e-02
A_51_P248122	Bbc3	BCL2 binding component 3	-1.77	3.04e-05	2.35e-02
A_51_P340027	Pappa	pregnancy-associated plasma protein A	-2.02	3.26e-05	2.35e-02
A_51_P452323	Nes	nestin	-1.85	3.28e-05	2.35e-02
A_51_P366867	Gas5	growth arrest specific 5	-1.46	3.29e-05	2.35e-02
A_51_P379798	Fdps	farnesyl diphosphate synthetase	1.28	3.37e-05	2.35e-02
A_52_P335606	Prima1	proline rich membrane anchor 1	1.25	3.40e-05	2.35e-02
A_51_P181297	Serpinb1a	serine (or cysteine) peptidase inhibitor, clade B, member 1a	1.98	3.59e-05	2.35e-02
A_52_P506217	Rhod	ras homolog family member D	-1.28	3.63e-05	2.35e-02
A_52_P208763	Ccl7	chemokine (C-C motif) ligand 7	-0.87	3.80e-05	2.39e-02
A_51_P493234	Cp	ceruloplasmin	-1.89	3.88e-05	2.39e-02
A_51_P355943	Mvd	mevalonate (diphospho) decarboxylase	1.23	4.04e-05	2.43e-02
A_52_P427024	Ldlr	low density lipoprotein receptor	1.83	4.19e-05	2.46e-02
A_51_P497937	Gjc2	gap junction protein, gamma 2	1.49	4.42e-05	2.49e-02
A_51_P508289	Ephx1	epoxide hydrolase 1, microsomal	-2.01	4.64e-05	2.49e-02
A_52_P416072	Ephx1	epoxide hydrolase 1, microsomal	-1.99	4.80e-05	2.49e-02
A_52_P634098	B230206H07Rik	RIKEN cDNA B230206H07 gene	1.50	4.81e-05	2.49e-02
A_51_P195153	Gtse1	G two S phase expressed protein 1	-1.01	4.83e-05	2.49e-02
A_52_P388072	Hmgcs1	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1	1.23	4.84e-05	2.49e-02
A_51_P117666	Snhg16	small nucleolar RNA host gene 16	-1.25	4.93e-05	2.49e-02
A_52_P111715	Galnt6	polypeptide N-acetylgalactosaminyltransferase 6	2.72	5.88e-05	2.79e-02
A_52_P630673	Gpr62	G protein-coupled receptor 62	2.50	5.98e-05	2.79e-02
A_52_P377160	Galnt6	polypeptide N-acetylgalactosaminyltransferase 6	1.22	6.01e-05	2.79e-02
A_51_P519251	Nupr1	nuclear protein transcription regulator 1	-3.63	6.02e-05	2.79e-02
A_52_P489295	Adamts1	a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 1	-1.59	6.07e-05	2.79e-02
A_52_P142154	Pcyt2	phosphate cytidylyltransferase 2, ethanolamine	1.28	6.19e-05	2.79e-02
A_51_P500984	Gadd45b	growth arrest and DNA-damage-inducible 45 beta	-1.31	6.43e-05	2.85e-02
A_52_P355169	Tnc	tenascin C	-1.71	6.56e-05	2.86e-02
A_51_P110341	Scgb3a1	secretoglobin, family 3A, member 1	-0.92	7.29e-05	3.02e-02
A_52_P406181	Nacad	NAC alpha domain containing	1.38	7.82e-05	3.19e-02
A_51_P258570	Klk6	kallikrein related-peptidase 6	2.91	8.19e-05	3.27e-02
A_52_P255849	Tlcd3a	TLC domain containing 3A	1.01	8.97e-05	3.47e-02
A_51_P222381	Tmeff1	transmembrane protein with EGF-like and two follistatin-like domains 1	1.11	9.49e-05	3.58e-02
A_51_P186703	Fbln5	fibulin 5	-1.34	1.04e-04	3.77e-02
A_51_P181312	Dcxr	dicarbonyl L-xylulose reductase	-1.37	1.06e-04	3.77e-02
A_52_P85040	Mog	myelin oligodendrocyte glycoprotein	2.67	1.06e-04	3.77e-02
A_52_P443705	Aen	apoptosis enhancing nuclease	-1.37	1.08e-04	3.77e-02
A_51_P480233	Nmral1	NmrA-like family domain containing 1	1.92	1.08e-04	3.77e-02
A_52_P633597	Rftn1	raftlin lipid raft linker 1	1.20	1.09e-04	3.77e-02
A_51_P411694	Carns1	carnosine synthase 1	1.40	1.13e-04	3.81e-02
A_52_P344160	Ccp110	centriolar coiled coil protein 110	1.70	1.13e-04	3.81e-02
A_52_P653684	Eprs	glutamyl-prolyl-tRNA synthetase	-1.11	1.15e-04	3.82e-02

A_52_P2710	Nat8f5	N-acetyltransferase 8 (GCN5-related) family member 5	-1.40	1.19e-04	3.82e-02
A_52_P670978	Nkain1	Na+/K+ transporting ATPase interacting 1	1.65	1.20e-04	3.82e-02
A_52_P597634	Fzd1	frizzled class receptor 1	-1.74	1.25e-04	3.82e-02
A_51_P225186	Calcrl	calcitonin receptor-like	-1.31	1.27e-04	3.82e-02
A_52_P326502	Sox21	SRY (sex determining region Y)-box 21	-1.13	1.27e-04	3.82e-02
A_51_P315411	Epb41l3	erythrocyte membrane protein band 4.1 like 3	1.44	1.28e-04	3.82e-02
A_52_P391000	Pde8a	phosphodiesterase 8A	1.53	1.41e-04	4.01e-02
A_51_P104418	Dusp10	dual specificity phosphatase 10	-1.54	1.42e-04	4.01e-02
A_51_P246903	Rps27l	ribosomal protein S27-like	-1.64	1.43e-04	4.01e-02
A_52_P627816	Tgm1	transglutaminase 1, K polypeptide	-3.27	1.44e-04	4.01e-02
A_52_P263068	Rhog	ras homolog family member G	1.12	1.45e-04	4.01e-02
A_51_P111612	Arrdc4	arrestin domain containing 4	-1.54	1.46e-04	4.01e-02
A_52_P624415	Opalin	oligodendrocytic myelin paranodal and inner loop protein	3.02	1.48e-04	4.03e-02
A_51_P381618	Pla1a	phospholipase A1 member A	-0.87	1.52e-04	4.05e-02
A_51_P252947	Mapk8ip1	mitogen-activated protein kinase 8 interacting protein 1	1.49	1.52e-04	4.05e-02
A_51_P482990	Arid5a	AT rich interactive domain 5A (MRF1-like)	-1.72	1.56e-04	4.09e-02
A_52_P503387	Trp53inp1	transformation related protein 53 inducible nuclear protein 1	-1.28	1.58e-04	4.09e-02
A_52_P512955	Anln	anillin, actin binding protein	1.45	1.59e-04	4.09e-02
A_51_P290921	Sytl2	synaptotagmin-like 2	1.22	1.66e-04	4.15e-02
A_51_P286737	Ccl2	chemokine (C-C motif) ligand 2	-2.41	1.66e-04	4.15e-02
A_51_P296608	Gadd45a	growth arrest and DNA-damage-inducible 45 alpha	-1.81	1.67e-04	4.15e-02
A_51_P209372	Msmo1	methylsterol monoxygenase 1	1.08	1.68e-04	4.15e-02
A_51_P499071	Mal	myelin and lymphocyte protein, T cell differentiation protein	2.81	1.71e-04	4.15e-02
A_52_P494168	Prr18	proline rich 18	2.21	1.71e-04	4.15e-02
A_52_P188172	Synj2	synaptojanin 2	1.37	1.73e-04	4.15e-02
A_51_P367060	Ifrd1	interferon-related developmental regulator 1	-1.28	1.74e-04	4.15e-02
A_51_P190740	Adssl1	adenylosuccinate synthetase like 1	1.81	1.78e-04	4.17e-02
A_51_P331805	Kctd15	potassium channel tetramerisation domain containing 15	-1.13	1.82e-04	4.20e-02
A_52_P641367	Desi1	desumoylating isopeptidase 1	1.52	1.83e-04	4.20e-02
A_51_P302503	Ppp1r15a	protein phosphatase 1, regulatory subunit 15A	-1.37	1.86e-04	4.24e-02
A_51_P107686	Foxc1	forkhead box C1	-1.14	1.90e-04	4.25e-02
A_51_P354354	Gal3st1	galactose-3-O-sulfotransferase 1	1.77	1.91e-04	4.25e-02
A_51_P108990	Cetn4	centrin 4	-1.40	1.93e-04	4.25e-02
A_52_P608322	Maff	v-maf musculoaponeurotic fibrosarcoma oncogene family, protein F (avian)	-2.24	1.95e-04	4.25e-02
A_52_P628702	Cntn2	contactin 2	1.94	1.96e-04	4.25e-02
A_52_P577329	Tmem88b	transmembrane protein 88B	2.10	1.97e-04	4.25e-02
A_51_P202857	Cdca7	cell division cycle associated 7	1.13	2.03e-04	4.33e-02
A_51_P406846	Nipal4	NIPA-like domain containing 4	1.10	2.04e-04	4.33e-02
A_51_P431737	Cth	cystathionase (cystathionine gamma-lyase)	-1.02	2.07e-04	4.33e-02
A_52_P393392	Insig1	insulin induced gene 1	0.96	2.09e-04	4.33e-02
A_51_P504863	Cdk18	cyclin-dependent kinase 18	1.32	2.10e-04	4.33e-02
A_51_P436269	Grin2c	glutamate receptor, ionotropic, NMDA2C (epsilon 3)	1.19	2.11e-04	4.33e-02
A_51_P426270	Mgp	matrix Gla protein	-1.46	2.23e-04	4.47e-02

A_52_P605266	Ptprd	protein tyrosine phosphatase, receptor type, D	1.49	2.24e-04	4.47e-02
A_51_P356967	Lgi3	leucine-rich repeat LGI family, member 3	1.76	2.25e-04	4.47e-02
A_52_P164709	Poc1a	POC1 centriolar protein A	1.10	2.30e-04	4.47e-02
A_51_P277994	Oas2	2'-5' oligoadenylate synthetase 2	-1.20	2.32e-04	4.47e-02
A_51_P201187	Pllp	plasma membrane proteolipid	1.65	2.33e-04	4.47e-02
A_52_P52357	Tor3a	torsin family 3, member A	-1.37	2.33e-04	4.47e-02
A_51_P268439	Mcam	melanoma cell adhesion molecule	1.29	2.34e-04	4.47e-02
A_52_P302496	Fah	fumarylacetoacetate hydrolase	1.30	2.36e-04	4.47e-02
A_51_P345975	Lpin3	lipin 3	-0.81	2.41e-04	4.48e-02
A_52_P268852	Helt	helt bHLH transcription factor	0.78	2.49e-04	4.56e-02
A_51_P252725	Gpc4	glypican 4	-1.73	2.49e-04	4.56e-02
A_51_P438527	Cyb5r1	cytochrome b5 reductase 1	-1.42	2.51e-04	4.56e-02
A_51_P211980	Rgs3	regulator of G-protein signaling 3	1.04	2.56e-04	4.57e-02
A_51_P111492	Nfil3	nuclear factor, interleukin 3, regulated	-1.05	2.57e-04	4.57e-02
A_51_P349205	Mbp	myelin basic protein	2.20	2.60e-04	4.59e-02
A_51_P480202	Dlx2	distal-less homeobox 2	1.21	2.81e-04	4.84e-02
A_51_P290986	Dhcr7	7-dehydrocholesterol reductase	1.23	2.83e-04	4.84e-02
A_52_P20977	Ldlrad4	low density lipoprotein receptor class A domain containing 4	1.12	2.87e-04	4.84e-02
A_51_P442501	Ano4	anoctamin 4	0.86	2.88e-04	4.84e-02
A_51_P175858	Cyb5r2	cytochrome b5 reductase 2	-0.63	2.89e-04	4.84e-02
A_52_P421344	Paqr5	progestin and adipoQ receptor family member V	-1.17	2.89e-04	4.84e-02
A_52_P193022	Hfe	homeostatic iron regulator	-1.41	2.90e-04	4.84e-02
A_51_P104710	Sspo	SCO-spondin	1.22	2.91e-04	4.84e-02
A_51_P117457	Dcaf12l2	DDB1 and CUL4 associated factor 12-like 2	-1.27	2.94e-04	4.86e-02
A_52_P384574	Stard4	StAR-related lipid transfer (START) domain containing 4	1.23	3.02e-04	4.92e-02
A_52_P598309	Zfas1	zinc finger, NFX1-type containing 1, antisense RNA 1	-1.17	3.07e-04	4.92e-02
A_52_P119997	Rhbdd1	rhomboid domain containing 1	-1.12	3.12e-04	4.92e-02
A_51_P424709	Nxph4	neurexophilin 4	0.93	3.13e-04	4.92e-02
A_51_P287617	Plekhh1	pleckstrin homology domain containing, family H (with MyTH4 domain) member 1	1.86	3.13e-04	4.92e-02
A_51_P325173	Tpm1	tropomyosin 1, alpha	0.92	3.14e-04	4.92e-02
A_51_P329928	Phlda3	pleckstrin homology like domain, family A, member 3	-1.33	3.19e-04	4.93e-02
A_52_P690855	Fndc11	fibronectin type III domain containing 11	1.31	3.20e-04	4.93e-02
A_51_P257282	Ttll7	tubulin tyrosine ligase-like family, member 7	1.07	3.24e-04	4.96e-02
A_51_P206585	Runx1	runt related transcription factor 1	-1.06	3.28e-04	4.97e-02
A_52_P493477	Serpinb1c	serine (or cysteine) peptidase inhibitor, clade B, member 1c	0.90	3.34e-04	4.97e-02
A_52_P7041	Odc1	ornithine decarboxylase, structural 1	-0.92	3.34e-04	4.97e-02
A_51_P486971	Tex52	testis expressed 52	0.91	3.35e-04	4.97e-02
A_51_P185575	Adamtsl4	ADAMTS-like 4	0.92	3.38e-04	4.97e-02
A_51_P308290	Cerox1	cytoplasmic endogenous regulator of oxidative phosphorylation 1	0.66	3.44e-04	4.97e-02
A_51_P484869	Gamt	guanidinoacetate methyltransferase	2.33	3.44e-04	4.97e-02
A_52_P198435	Rasgrp3	RAS, guanyl releasing protein 3	1.08	3.48e-04	4.97e-02
A_51_P308298	Myl9	myosin, light polypeptide 9, regulatory	-1.26	3.49e-04	4.97e-02
A_52_P121675	Cebpg	CCAAT/enhancer binding protein (C/EBP), gamma	-1.13	3.49e-04	4.97e-02
A_52_P31814	1110038B12Rik	RIKEN cDNA 1110038B12 gene	-1.36	3.53e-04	4.97e-02
A_52_P335478	Pole4	polymerase (DNA-directed), epsilon 4 (p12 subunit)	-0.95	3.58e-04	4.97e-02

A_52_P63553	Cebpb	CCAAT/enhancer binding protein (C/EBP), beta	-1.33	3.59e-04	4.97e-02
A_52_P485007	Abca2	ATP-binding cassette, sub-family A (ABC1), member 2	1.57	3.63e-04	4.97e-02
A_51_P255832	Omg	oligodendrocyte myelin glycoprotein	0.92	3.63e-04	4.97e-02
A_51_P432380	Aplp1	amyloid beta (A4) precursor-like protein 1	1.21	3.68e-04	4.97e-02
A_51_P398260	Tppp	tubulin polymerization promoting protein	0.94	3.68e-04	4.97e-02
A_52_P517683	Tagln	transgelin	-1.76	3.73e-04	4.97e-02
A_51_P282896	Mast4	microtubule associated serine/threonine kinase family member 4	1.53	3.75e-04	4.97e-02
A_51_P105927	Rasl12	RAS-like, family 12	0.89	3.77e-04	4.97e-02
A_51_P212057	Serpinb1c	serine (or cysteine) peptidase inhibitor, clade B, member 1c	1.65	3.77e-04	4.97e-02

Table 4.2. DEGs identified in the microglia obtained from mice treated with cuprizone for 4 weeks compared with microglia obtained from control mice.

Probe ID	Symbol	Gene name	Log2 fold change	p-value	Adjusted p-value
10583056	Mmp12	matrix metallopeptidase 12	2.63	0.00	0.01
10414360	Lgals3	lectin, galactose binding, soluble 3	2.15	0.00	0.01
10526853	Fam20c	family with sequence similarity 20, member C	2.22	0.00	0.03
10371770	Gas2l3	growth arrest-specific 2 like 3	1.54	0.00	0.03
10357472	Cxcr4	chemokine (C-X-C motif) receptor 4	1.35	0.00	0.03
10517336	Clic4	chloride intracellular channel 4 (mitochondrial)	1.13	0.00	0.03
10548375	Clec7a	C-type lectin domain family 7, member a	2.47	0.00	0.03
10572130	Lpl	lipoprotein lipase	3.04	0.00	0.03
10548333	Cd69	CD69 antigen	1.27	0.00	0.04
10557895	Itgax	integrin alpha X	2.74	0.00	0.04
10349661	Rab7b	RAB7B, member RAS oncogene family	1.33	0.00	0.04
10548385	Olr1	oxidized low density lipoprotein (lectin-like) receptor 1	1.83	0.00	0.04

Table 4.3. DEGs identified in the OPCs obtained from mice treated with cuprizone for 5 weeks compared with OPCs obtained from control mice. Due to the large number of DEGs only those with an adjusted p-value<0.001 are presented.

Probe ID	Symbol	Gene name	Log2 fold change	p-value	Adjusted p-value
A_55_P1986296	Tagln2	Mus musculus transgelin 2 (Tagln2), mRNA [NM_178598]	5.16	1.79e-12	5.74e-08
A_55_P2105858	Atf5	Mus musculus activating transcription factor 5 (Atf5), transcript variant 1, mRNA [NM_030693]	3.27	2.35e-11	3.76e-07
A_66_P106661	Slc7a1	Mus musculus solute carrier family 7 (cationic amino acid transporter, y+ system), member 1 (Slc7a1), mRNA [NM_007513]	4.35	3.56e-11	3.80e-07
A_51_P241995	Col5a3	Mus musculus collagen, type V, alpha 3 (Col5a3), mRNA [NM_016919]	4.25	1.43e-10	1.15e-06
A_52_P1197913	Gadd45b	Mus musculus growth arrest and DNA-damage-inducible 45 beta (Gadd45b), mRNA [NM_008655]	3.67	2.49e-10	1.60e-06

A_51_P363947	Cdkn1a	Mus musculus cyclin-dependent kinase inhibitor 1A (P21) (Cdkn1a), transcript variant 1, mRNA [NM_007669]	5.83	4.29e-10	2.29e-06
A_66_P111562	Ccnd1	Mus musculus cyclin D1 (Ccnd1), mRNA [NM_007631]	3.40	5.58e-10	2.38e-06
A_55_P2009988	Trib3	Mus musculus tribbles homolog 3 (Drosophila) (Trib3), mRNA [NM_175093]	7.23	5.93e-10	2.38e-06
A_55_P2136880	Ppp1r15a	Mus musculus protein phosphatase 1, regulatory (inhibitor) subunit 15A (Ppp1r15a), mRNA [NM_008654]	2.96	7.51e-10	2.67e-06
A_51_P367866	Egr1	Mus musculus early growth response 1 (Egr1), mRNA [NM_007913]	2.49	9.52e-10	3.05e-06
A_51_P519251	Nupr1	Mus musculus nuclear protein 1 (Nupr1), mRNA [NM_019738]	4.86	1.13e-09	3.22e-06
A_51_P403536	Ltbp4	Mus musculus latent transforming growth factor beta binding protein 4 (Ltbp4), transcript variant 1, mRNA [NM_175641]	2.73	1.21e-09	3.22e-06
A_51_P248122	Bbc3	Mus musculus BCL2 binding component 3 (Bbc3), mRNA [NM_133234]	2.91	1.48e-09	3.64e-06
A_55_P2113051	Fosb	Mus musculus FBJ osteosarcoma oncogene B (Fosb), mRNA [NM_008036]	2.54	3.51e-09	6.85e-06
A_55_P2034864	Tubb2b	Mus musculus tubulin, beta 2B (Tubb2b), mRNA [NM_023716]	2.92	3.64e-09	6.85e-06
A_51_P474459	Socs3	Mus musculus suppressor of cytokine signaling 3 (Socs3), mRNA [NM_007707]	3.16	3.85e-09	6.85e-06
A_51_P392687	Vim	Mus musculus vimentin (Vim), mRNA [NM_011701]	3.44	3.21e-09	6.85e-06
A_55_P2121608	Sox4	Transcription factor SOX-4 [Source:UniProtKB/Swiss-Prot;Acc:Q06831] [ENSMUST00000067230]	3.21	3.84e-09	6.85e-06
A_55_P2162204	Kctd15	Mus musculus potassium channel tetramerisation domain containing 15 (Kctd15), mRNA [NM_146188]	2.95	5.25e-09	8.85e-06
A_51_P315904	Gadd45g	Mus musculus growth arrest and DNA-damage-inducible 45 gamma (Gadd45g), mRNA [NM_011817]	4.09	6.27e-09	1.01e-05
A_51_P131408	Tnfrsf12a	Mus musculus tumor necrosis factor receptor superfamily, member 12a (Tnfrsf12a), transcript variant 1, mRNA [NM_013749]	3.42	6.65e-09	1.01e-05
A_55_P1959748	Asns	Mus musculus asparagine synthetase (Asns), mRNA [NM_012055]	4.47	7.35e-09	1.07e-05
A_55_P2127139	Hist1h3d	Mus musculus histone cluster 1, H3d (Hist1h3d), mRNA [NM_178204]	1.78	8.52e-09	1.19e-05
A_55_P2122020	Klf4	Mus musculus Kruppel-like factor 4 (gut) (Klf4), mRNA [NM_010637]	3.07	9.31e-09	1.24e-05
A_51_P394190	Lmo4	Mus musculus LIM domain only 4 (Lmo4), transcript variant 1, mRNA [NM_010723]	2.61	1.06e-08	1.35e-05
A_51_P490023	Tubb2a	Mus musculus tubulin, beta 2A (Tubb2a), mRNA [NM_009450]	2.52	1.10e-08	1.35e-05
A_51_P483118	Hmga1	Mus musculus high mobility group AT-hook 1 (Hmga1), transcript variant 1, mRNA [NM_016660]	2.66	1.20e-08	1.43e-05
A_51_P206405	Ptprz1	Mus musculus protein tyrosine phosphatase, receptor type Z, polypeptide 1 (Ptprz1), mRNA [NM_001081306]	2.62	1.41e-08	1.52e-05
A_55_P2076273	Gm12260	PREDICTED: Mus musculus similar to histone H3 (LOC382523), mRNA [XM_905850]	2.01	1.46e-08	1.52e-05
A_55_P2162910	Rtn1	Mus musculus reticulon 1 (Rtn1), transcript variant 1, mRNA [NM_153457]	3.15	1.47e-08	1.52e-05
A_55_P1955869	Gm9315	PREDICTED: Mus musculus predicted gene, EG668714 (EG668714), mRNA [XM_001003263]	-3.25	1.69e-08	1.64e-05
A_51_P352968	Marcks	Mus musculus myristoylated alanine rich protein kinase C substrate (Marcks), mRNA [NM_008538]	3.84	1.79e-08	1.68e-05
A_55_P2035320	Nfil3	Mus musculus nuclear factor, interleukin 3, regulated (Nfil3), mRNA [NM_017373]	2.10	1.86e-08	1.70e-05
A_55_P1964960	Il33	Mus musculus interleukin 33 (Il33), transcript variant 1, mRNA [NM_001164724]	-1.81	2.24e-08	1.99e-05
A_55_P2141860	Aen	Mus musculus apoptosis enhancing nuclease (Aen), transcript variant 1, mRNA [NM_026531]	2.47	2.59e-08	2.24e-05

A_55_P2003541	Nrcam	Mus musculus neuron-glia-CAM-related cell adhesion molecule (Nrcam), transcript variant 1, mRNA [NM_176930]	2.55	2.81e-08	2.35e-05
A_51_P258690	Scrg1	Mus musculus scrapie responsive gene 1 (Scrg1), mRNA [NM_009136]	2.72	2.86e-08	2.35e-05
A_55_P2006008	Serpinb1a	Mus musculus serine (or cysteine) peptidase inhibitor, clade B, member 1a (Serpinb1a), mRNA [NM_025429]	-1.88	3.04e-08	2.43e-05
A_55_P1971599	Bcan	Mus musculus brevican (Bcan), transcript variant 1, mRNA [NM_007529]	3.27	3.35e-08	2.54e-05
A_51_P314397	Crip2	Mus musculus cysteine rich protein 2 (Crip2), mRNA [NM_024223]	2.10	3.41e-08	2.54e-05
A_52_P76034	Rcc2	Mus musculus regulator of chromosome condensation 2 (Rcc2), mRNA [NM_173867]	2.24	3.57e-08	2.60e-05
A_55_P1959485	LOC634933	PREDICTED: Mus musculus similar to protein phosphatase 1, catalytic subunit (LOC634933), mRNA [XM_909811]	-2.90	3.81e-08	2.68e-05
A_51_P439612	Dnajb2	Mus musculus DnaJ (Hsp40) homolog, subfamily B, member 2 (Dnajb2), transcript variant 1, mRNA [NM_020266]	-1.85	3.85e-08	2.68e-05
A_55_P2080860	Cmtm5	Mus musculus CKLF-like MARVEL transmembrane domain containing 5 (Cmtm5), mRNA [NM_026066]	-1.96	3.94e-08	2.68e-05
A_51_P501844	Cyp26b1	Mus musculus cytochrome P450, family 26, subfamily b, polypeptide 1 (Cyp26b1), mRNA [NM_175475]	2.50	4.13e-08	2.75e-05
A_66_P129048	2610002J02Rik	Mus musculus RIKEN cDNA 2610002J02 gene (2610002J02Rik), mRNA [NM_001033134]	1.98	4.86e-08	3.18e-05
A_52_P262219	Fos	Mus musculus FBJ osteosarcoma oncogene (Fos), mRNA [NM_010234]	2.36	4.97e-08	3.19e-05
A_52_P665675	Abca1	Mus musculus ATP-binding cassette, sub-family A (ABC1), member 1 (Abca1), mRNA [NM_013454]	2.24	5.28e-08	3.26e-05
A_55_P2117710	Snhg1	Mus musculus small nucleolar RNA host gene (non-protein coding) 1 (Snhg1), non-coding RNA [NR_002896]	1.93	5.34e-08	3.26e-05
A_66_P105032	Gm13889	Mus musculus predicted gene 13889 (Gm13889), mRNA [NM_001145034]	2.15	5.74e-08	3.38e-05
A_55_P2008061	Itpr2	Mus musculus inositol 1,4,5-triphosphate receptor 2 (Itpr2), transcript variant 1, mRNA [NM_019923]	2.36	5.80e-08	3.38e-05
A_55_P2098598	Btg1	Mus musculus B-cell translocation gene 1, anti-proliferative (Btg1), mRNA [NM_007569]	3.03	6.03e-08	3.45e-05
A_51_P242414	Micall1	Mus musculus microtubule associated monoxygenase, calponin and LIM domain containing -like 1 (Micall1), mRNA [NM_177461]	-1.59	6.50e-08	3.65e-05
A_51_P398260	Tppp	Mus musculus tubulin polymerization promoting protein (Tppp), mRNA [NM_182839]	-1.53	6.77e-08	3.74e-05
A_55_P2024704	Cpe	Mus musculus carboxypeptidase E (Cpe), mRNA [NM_013494]	1.88	6.99e-08	3.80e-05
A_51_P198434	H2-K1	Mus musculus histocompatibility 2, K1, K region (H2-K1), transcript variant 1, mRNA [NM_001001892]	2.11	7.26e-08	3.87e-05
A_55_P1986998	Enoph1	Mus musculus enolase-phosphatase 1 (Enoph1), transcript variant 1, mRNA [NM_026421]	-1.63	7.37e-08	3.87e-05
A_51_P355151	Camk2n2	Mus musculus calcium/calmodulin-dependent protein kinase II inhibitor 2 (Camk2n2), mRNA [NM_028420]	2.32	8.05e-08	4.11e-05
A_65_P19395	H2-D1	Mus musculus histocompatibility 2, D region locus 1 (H2-D1), mRNA [NM_010380]	2.84	8.08e-08	4.11e-05
A_55_P2042923	Sgk2	Mus musculus serum/glucocorticoid regulated kinase 2 (Sgk2), mRNA [NM_013731]	-2.66	9.13e-08	4.47e-05
A_52_P439263	Ugt8a	Mus musculus UDP galactosyltransferase 8A (Ugt8a), mRNA [NM_011674]	-1.83	9.19e-08	4.47e-05
A_55_P2047559	6330503K22Rik	Mus musculus RIKEN cDNA 6330503K22 gene (6330503K22Rik), mRNA [NM_182995]	-1.97	9.22e-08	4.47e-05
A_55_P2072373	Msn	Mus musculus moesin (Msn), mRNA [NM_010833]	2.27	9.44e-08	4.51e-05
A_51_P170463	Gpr17	Mus musculus G protein-coupled receptor 17 (Gpr17), mRNA	2.93	9.61e-08	4.53e-05

		[NM_001025381]			
A_55_P2059164	H3f3b	Mus musculus H3 histone, family 3B (H3f3b), mRNA [NM_008211]	1.49	1.01e-07	4.55e-05
A_66_P134542	Anln	Mus musculus anillin, actin binding protein (Anln), mRNA [NM_028390]	-1.82	1.01e-07	4.55e-05
A_55_P1972575	Tmeff1	Mus musculus transmembrane protein with EGF-like and two follistatin-like domains 1 (Tmeff1), mRNA [NM_021436]	-1.77	1.02e-07	4.55e-05
A_55_P2130388	Mical1	Mus musculus microtubule associated monoxygenase, calponin and LIM domain containing 1 (Mical1), transcript variant 1, mRNA [NM_138315]	2.04	1.00e-07	4.55e-05
A_55_P2075070	S1pr5	Mus musculus sphingosine-1-phosphate receptor 5 (S1pr5), mRNA [NM_053190]	-1.79	1.13e-07	4.91e-05
A_51_P472901	Slc3a2	Mus musculus solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2 (Slc3a2), transcript variant 2, mRNA [NM_008577]	1.76	1.25e-07	5.35e-05
A_55_P2002578	Ephx1	Mus musculus epoxide hydrolase 1, microsomal (Ephx1), mRNA [NM_010145]	2.66	1.30e-07	5.48e-05
A_66_P111430	2410006H16Rik	Mus musculus RIKEN cDNA 2410006H16 gene (2410006H16Rik), non-coding RNA [NR_030738]	2.56	1.34e-07	5.48e-05
A_51_P269084	Chchd10	Mus musculus coiled-coil-helix-coiled-coil-helix domain containing 10 (Chchd10), mRNA [NM_175329]	2.85	1.35e-07	5.48e-05
A_51_P502614	Dusp6	Mus musculus dual specificity phosphatase 6 (Dusp6), mRNA [NM_026268]	2.49	1.35e-07	5.48e-05
A_55_P2136501	Midn	Mus musculus midnolin (Midn), mRNA [NM_021565]	2.56	1.43e-07	5.53e-05
A_55_P2126448	1810032O08Rik	Mus musculus RIKEN cDNA 1810032O08 gene (1810032O08Rik), transcript variant 3, non-coding RNA [NR_027821]	1.93	1.45e-07	5.53e-05
A_55_P2066697	Trim47	Mus musculus tripartite motif-containing 47 (Trim47), mRNA [NM_172570]	2.15	1.42e-07	5.53e-05
A_55_P2345853	3830612M24	Mus musculus 18 days pregnant adult female placenta and extra embryonic tissue cDNA, RIKEN full-length enriched library, clone:3830612M24 product:unclassifiable, full insert sequence. [AK028406]	2.88	1.43e-07	5.53e-05
A_51_P106059	Traf4	Mus musculus TNF receptor associated factor 4 (Traf4), mRNA [NM_009423]	2.47	1.44e-07	5.53e-05
A_51_P451346	Klf6	Mus musculus Kruppel-like factor 6 (Klf6), mRNA [NM_011803]	1.65	1.51e-07	5.71e-05
A_55_P2006525	Adamtsl4	Mus musculus ADAMTS-like 4 (Adamtsl4), mRNA [NM_144899]	-2.48	1.59e-07	5.90e-05
A_55_P1983999	Pppde2	Mus musculus PPPDE peptidase domain containing 2 (Pppde2), mRNA [NM_134095]	-2.17	1.60e-07	5.90e-05
A_52_P137765	Lmna	Mus musculus lamin A (Lmna), transcript variant 2, mRNA [NM_019390]	1.91	1.64e-07	5.90e-05
A_52_P598309	1500012F01Rik	Mus musculus RIKEN cDNA 1500012F01 gene (1500012F01Rik), mRNA [NM_001081005]	1.68	1.65e-07	5.90e-05
A_55_P2078633	C4b	Mus musculus complement component 4B (Childo blood group) (C4b), mRNA [NM_009780]	2.09	1.66e-07	5.90e-05
A_52_P497188	Prrg1	Mus musculus proline rich Gla (G-carboxyglutamic acid) 1 (Prrg1), transcript variant 1, mRNA [NM_027322]	-1.95	1.68e-07	5.90e-05
A_55_P2117119	Efhd1	Mus musculus EF hand domain containing 1 (Efhd1), mRNA [NM_028889]	-1.93	1.75e-07	6.08e-05
A_66_P126332	Zfp703	Mus musculus zinc finger protein 703 (Zfp703), transcript variant 2, mRNA [NM_001110508]	2.88	1.79e-07	6.17e-05
A_51_P409429	Aars	Mus musculus alanyl-tRNA synthetase (Aars), mRNA [NM_146217]	1.83	1.82e-07	6.22e-05
A_51_P200561	4930506M07Rik	Mus musculus RIKEN cDNA 4930506M07 gene (4930506M07Rik), transcript variant 2, mRNA [NM_175172]	-2.42	2.15e-07	7.10e-05
A_52_P533146	Ddit3	Mus musculus DNA-damage inducible transcript 3 (Ddit3), mRNA [NM_007837]	2.26	2.15e-07	7.10e-05

A_55_P2150757	Gzmm	Mus musculus granzyme M (lymphocyte met-ase 1) (Gzmm), mRNA [NM_008504]	1.78	2.35e-07	7.67e-05
A_52_P452689	Atf3	Mus musculus activating transcription factor 3 (Atf3), mRNA [NM_007498]	2.99	2.45e-07	7.92e-05
A_55_P2083889	Pea15a	Mus musculus phosphoprotein enriched in astrocytes 15A (Pea15a), transcript variant 2, mRNA [NM_011063]	-1.57	2.48e-07	7.92e-05
A_55_P2012389	Sfxn3	Mus musculus sideroflexin 3 (Sfxn3), mRNA [NM_053197]	1.61	2.50e-07	7.92e-05
A_51_P225793	Prr5l	Mus musculus proline rich 5 like (Prr5l), transcript variant 2, mRNA [NM_175181]	-1.10	2.57e-07	8.06e-05
A_51_P140690	Stmn3	Mus musculus stathmin-like 3 (Stmn3), mRNA [NM_009133]	2.06	2.69e-07	8.38e-05
A_55_P2091359	Padi2	Mus musculus peptidyl arginine deiminase, type II (Padi2), mRNA [NM_008812]	-1.75	2.74e-07	8.42e-05
A_55_P2142072	Synj2	Mus musculus synaptojanin 2 (Synj2), transcript variant 3, mRNA [NM_011523]	-2.01	2.76e-07	8.42e-05
A_55_P2017645	Tap2	Mus musculus transporter 2, ATP-binding cassette, sub-family B (MDR/TAP) (Tap2), mRNA [NM_011530]	2.09	3.10e-07	9.37e-05
A_51_P129012	B2m	Mus musculus beta-2 microglobulin (B2m), mRNA [NM_009735]	2.18	3.14e-07	9.39e-05
A_55_P1955393	Sept7	Mus musculus septin 7 (Sept7), mRNA [NM_009859]	-1.23	3.30e-07	9.61e-05
A_55_P2033376	1810041L15Rik	Mus musculus RIKEN cDNA 1810041L15 gene (1810041L15Rik), mRNA [NM_001163145]	2.79	3.38e-07	9.76e-05
A_55_P2149931	Arap2	Mus musculus ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 2 (Arap2), mRNA [NM_178407]	1.73	3.54e-07	1.00e-04
A_66_P135106	Slco3a1	Mus musculus solute carrier organic anion transporter family, member 3a1 (Slco3a1), transcript variant 2, mRNA [NM_001038643]	-1.58	3.59e-07	1.00e-04
A_55_P2033362	Egr2	Mus musculus early growth response 2 (Egr2), mRNA [NM_010118]	2.47	3.64e-07	1.00e-04
A_55_P1958678	Brd2	Mus musculus bromodomain containing 2 (Brd2), transcript variant 2, mRNA [NM_001025387]	1.30	3.64e-07	1.00e-04
A_51_P110759	Slc1a1	Mus musculus solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1 (Slc1a1), mRNA [NM_009199]	2.43	3.65e-07	1.00e-04
A_51_P493987	Moxd1	Mus musculus monooxygenase, DBH-like 1 (Moxd1), mRNA [NM_021509]	4.18	3.58e-07	1.00e-04
A_55_P1961461	Bnip3l	Mus musculus BCL2/adenovirus E1B interacting protein 3-like (Bnip3l), mRNA [NM_009761]	-1.14	3.69e-07	1.00e-04
A_55_P1960097	Epb4.1l3	Mus musculus erythrocyte protein band 4.1-like 3 (Epb4.1l3), mRNA [NM_013813]	-1.74	4.05e-07	1.08e-04
A_51_P246317	Mt2	Mus musculus metallothionein 2 (Mt2), mRNA [NM_008630]	3.35	4.37e-07	1.15e-04
A_55_P2067942	D16Ertd472e	Mus musculus DNA segment, Chr 16, ERATO Doi 472, expressed (D16Ertd472e), mRNA [NM_025967]	-1.33	4.61e-07	1.19e-04
A_55_P2032966	Hmgcs1	Mus musculus 3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1 (Hmgcs1), mRNA [NM_145942]	-1.74	4.75e-07	1.22e-04
A_55_P2108988	Kcnip3	Mus musculus Kv channel interacting protein 3, calsenilin (Kcnip3), transcript variant 2, mRNA [NM_001111331]	2.78	4.89e-07	1.23e-04
A_55_P2118268	Chpf	Mus musculus chondroitin polymerizing factor (Chpf), transcript variant 2, mRNA [NM_001001565]	1.59	4.93e-07	1.23e-04
A_51_P330428	Eif4ebp1	Mus musculus eukaryotic translation initiation factor 4E binding protein 1 (Eif4ebp1), mRNA [NM_007918]	3.88	4.94e-07	1.23e-04
A_55_P2101088	Slc5a11	Mus musculus solute carrier family 5 (sodium/glucose cotransporter), member 11 (Slc5a11), mRNA [NM_146198]	-1.96	5.27e-07	1.29e-04
A_51_P507053	Slc38a1	Mus musculus solute carrier family 38, member 1 (Slc38a1), transcript variant 1, mRNA [NM_134086]	2.12	5.50e-07	1.33e-04
A_52_P590396	Sort1	Mus musculus sortilin 1 (Sort1), mRNA [NM_019972]	-1.43	5.55e-07	1.34e-04
A_51_P259975	Aspa	Mus musculus aspartoacylase (Aspa), mRNA [NM_023113]	-1.49	5.68e-07	1.34e-04

A_55_P1998651	Entpd5	Mus musculus ectonucleoside triphosphate diphosphohydrolase 5 (Entpd5), transcript variant 2, mRNA [NM_001026214]	-1.66	5.67e-07	1.34e-04
A_55_P2227321	Ptprd	Mus musculus protein tyrosine phosphatase, receptor type, D (Ptprd), transcript variant b, mRNA [NM_011211]	-2.27	5.68e-07	1.34e-04
A_55_P1978511	H2-Q7	Mus musculus histocompatibility 2, Q region locus 7 (H2-Q7), mRNA [NM_010394]	2.33	6.04e-07	1.39e-04
A_55_P2051334	Gm7035	Mus musculus predicted gene 7035 (Gm7035), non-coding RNA [NR_004446]	1.51	6.26e-07	1.43e-04
A_55_P2045802	Nelf	Mus musculus nasal embryonic LHRH factor (Nelf), transcript variant 1, mRNA [NM_001039386]	-1.15	7.13e-07	1.61e-04
A_55_P1985793	Dock6	Mus musculus dedicator of cytokinesis 6 (Dock6), mRNA [NM_177030]	1.59	7.26e-07	1.62e-04
A_55_P2165869	Cebpb	Mus musculus CCAAT/enhancer binding protein (C/EBP), beta (Cebpb), mRNA [NM_009883]	2.33	7.27e-07	1.62e-04
A_51_P464300	Gdf1	Mus musculus growth differentiation factor 1 (Gdf1), transcript variant 2, mRNA [NM_008107]	1.61	7.42e-07	1.64e-04
A_51_P426739	Gpt	Mus musculus glutamic pyruvic transaminase, soluble (Gpt), mRNA [NM_182805]	-1.77	7.75e-07	1.70e-04
A_55_P2018847	Crlf2	Mus musculus cytokine receptor-like factor 2 (Crlf2), transcript variant 1, mRNA [NM_001164735]	1.81	7.87e-07	1.72e-04
A_66_P100249	Snhg12	Mus musculus small nucleolar RNA host gene 12 (Snhg12), non-coding RNA [NR_029468]	1.80	8.03e-07	1.74e-04
A_52_P373694	Jph4	Mus musculus junctophilin 4 (Jph4), transcript variant a, mRNA [NM_177049]	-3.81	8.19e-07	1.76e-04
A_51_P237754	H2-T23	Mus musculus histocompatibility 2, T region locus 23 (H2-T23), mRNA [NM_010398]	1.92	8.49e-07	1.81e-04
A_55_P1999361	Dip2a	Mus musculus DIP2 disco-interacting protein 2 homolog A (Drosophila) (Dip2a), mRNA [NM_001081419]	-1.40	8.52e-07	1.81e-04
A_51_P172344	Foxn3	Mus musculus forkhead box N3 (Foxn3), mRNA [NM_183186]	-1.41	8.97e-07	1.89e-04
A_55_P1971963	Tmem176b	Mus musculus transmembrane protein 176B (Tmem176b), transcript variant 1, mRNA [NM_023056]	2.76	9.23e-07	1.93e-04
A_66_P121369	Gars	Mus musculus glycyl-tRNA synthetase (Gars), mRNA [NM_180678]	1.05	9.83e-07	2.05e-04
A_51_P358354	Jam3	Mus musculus junction adhesion molecule 3 (Jam3), mRNA [NM_023277]	-0.98	1.07e-06	2.20e-04
A_51_P520384	Atp1b3	Mus musculus ATPase, Na+/K+ transporting, beta 3 polypeptide (Atp1b3), mRNA [NM_007502]	-1.27	1.07e-06	2.20e-04
A_52_P597634	Fzd1	Mus musculus frizzled homolog 1 (Drosophila) (Fzd1), mRNA [NM_021457]	2.26	1.12e-06	2.28e-04
A_55_P1960735	Gdf15	Mus musculus growth differentiation factor 15 (Gdf15), mRNA [NM_011819]	5.28	1.12e-06	2.28e-04
A_55_P1956672	Rab34	Mus musculus RAB34, member of RAS oncogene family (Rab34), transcript variant 1, mRNA [NM_033475]	1.69	1.13e-06	2.28e-04
A_55_P1989921	Eml2	Mus musculus echinoderm microtubule associated protein like 2 (Eml2), transcript variant 1, mRNA [NM_028153]	-1.66	1.19e-06	2.39e-04
A_51_P105927	Rasl12	Mus musculus RAS-like, family 12 (Rasl12), transcript variant 1, mRNA [NM_001033158]	-1.93	1.21e-06	2.40e-04
A_55_P1979684	Rhoc	Mus musculus ras homolog gene family, member C (Rhoc), mRNA [NM_007484]	1.44	1.23e-06	2.42e-04
A_55_P1996674	Itih3	Mus musculus inter-alpha trypsin inhibitor, heavy chain 3 (Itih3), mRNA [NM_008407]	-2.29	1.32e-06	2.57e-04
A_51_P122035	Nipa1	Mus musculus non imprinted in Prader-Willi/Angelman syndrome 1 homolog (human) (Nipa1), mRNA [NM_153578]	-1.76	1.31e-06	2.57e-04
A_55_P2099358	Cars	Mus musculus cysteinyl-tRNA synthetase (Cars), mRNA [NM_013742]	1.43	1.35e-06	2.60e-04
A_55_P2102515	Daam1	Mus musculus dishevelled associated activator of	-1.85	1.36e-06	2.60e-04

		morphogenesis 1 (Daam1), transcript variant 1, mRNA [NM_026102]			
A_55_P2256163	4930506C21Rik	Mus musculus adult male testis cDNA, RIKEN full-length enriched library, clone:4930506C21 product:unclassifiable, full insert sequence. [AK015714]	-2.15	1.43e-06	2.72e-04
A_51_P438841	Ctnna2	Mus musculus catenin (cadherin associated protein), alpha 2 (Ctnna2), transcript variant 2, mRNA [NM_009819]	-1.29	1.46e-06	2.76e-04
A_51_P444447	Cebpd	Mus musculus CCAAT/enhancer binding protein (C/EBP), delta (Cebpd), mRNA [NM_007679]	2.49	1.49e-06	2.77e-04
A_52_P624415	Opalin	Mus musculus oligodendrocytic myelin paranodal and inner loop protein (Opalin), mRNA [NM_153520]	-1.99	1.50e-06	2.77e-04
A_51_P492125	Ciapin1	Mus musculus cytokine induced apoptosis inhibitor 1 (Ciapin1), mRNA [NM_134141]	1.38	1.50e-06	2.77e-04
A_55_P2227355	Ptpro	Mus musculus protein tyrosine phosphatase, receptor type, O (Ptpro), transcript variant 1, mRNA [NM_011216]	1.77	1.52e-06	2.77e-04
A_55_P2030938	Trim59	Mus musculus tripartite motif-containing 59 (Trim59), mRNA [NM_025863]	-1.11	1.52e-06	2.77e-04
A_51_P296608	Gadd45a	Mus musculus growth arrest and DNA-damage-inducible 45 alpha (Gadd45a), mRNA [NM_007836]	2.07	1.53e-06	2.77e-04
A_51_P339540	Cdkn1c	Mus musculus cyclin-dependent kinase inhibitor 1C (P57) (Cdkn1c), transcript variant 2, mRNA [NM_009876]	1.62	1.58e-06	2.84e-04
A_65_P02958	Rnf13	Mus musculus ring finger protein 13 (Rnf13), transcript variant 1, mRNA [NM_001113413]	-1.09	1.62e-06	2.88e-04
A_55_P2032818	Trim2	Mus musculus tripartite motif-containing 2 (Trim2), mRNA [NM_030706]	-0.91	1.61e-06	2.88e-04
A_52_P489295	Adamts1	Mus musculus a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 1 (Adamts1), mRNA [NM_009621]	1.36	1.63e-06	2.88e-04
A_51_P297336	Chmp7	Mus musculus CHMP family, member 7 (Chmp7), mRNA [NM_134078]	-1.27	1.64e-06	2.89e-04
A_55_P2086128	Fa2h	Mus musculus fatty acid 2-hydroxylase (Fa2h), mRNA [NM_178086]	-1.43	1.69e-06	2.96e-04
A_51_P436817	Dos	Mus musculus downstream of Stk11 (Dos), mRNA [NM_015761]	1.52	1.80e-06	3.14e-04
A_52_P541833	Vps37b	Mus musculus vacuolar protein sorting 37B (yeast) (Vps37b), mRNA [NM_177876]	1.52	1.83e-06	3.17e-04
A_55_P2014224	Sema5a	Mus musculus sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5A (Sema5a), mRNA [NM_009154]	2.11	1.84e-06	3.17e-04
A_55_P2040170	Pmp22	Mus musculus peripheral myelin protein 22 (Pmp22), mRNA [NM_008885]	-1.34	1.87e-06	3.20e-04
A_55_P2031496	Rufy3	Mus musculus RUN and FYVE domain containing 3 (Rufy3), mRNA [NM_027530]	-1.05	1.88e-06	3.20e-04
A_55_P2121856	Ier5l	Mus musculus immediate early response 5-like (Ier5l), mRNA [NM_030244]	2.96	1.89e-06	3.21e-04
A_51_P251352	Slc25a13	Mus musculus solute carrier family 25 (mitochondrial carrier, adenine nucleotide translocator), member 13 (Slc25a13), nuclear gene encoding mitochondrial protein, mRNA [NM_015829]	-1.83	1.93e-06	3.24e-04
A_55_P2167999	Ldlr	Mus musculus low density lipoprotein receptor (Ldlr), mRNA [NM_010700]	-1.61	2.00e-06	3.34e-04
A_55_P1977633	6430527G18Rik	Mus musculus RIKEN cDNA 6430527G18 gene (6430527G18Rik), mRNA [NM_145836]	1.53	2.08e-06	3.45e-04
A_51_P463765	Timp3	Mus musculus tissue inhibitor of metalloproteinase 3 (Timp3), mRNA [NM_011595]	2.30	2.09e-06	3.45e-04
A_55_P2094896	Phyhd1	Mus musculus phytanoyl-CoA dioxygenase domain containing 1 (Phyhd1), mRNA [NM_172267]	2.29	2.11e-06	3.47e-04
A_66_P105046	Il18	Mus musculus interleukin 18 (Il18), mRNA [NM_008360]	-1.21	2.13e-06	3.48e-04

A_55_P1961863	Pcdhga9	Mus musculus protocadherin gamma subfamily A, 9 (Pcdhga9), mRNA [NM_033592]	1.25	2.17e-06	3.53e-04
A_55_P2058942	Aldh3b1	Mus musculus aldehyde dehydrogenase 3 family, member B1 (Aldh3b1), mRNA [NM_026316]	-1.37	2.20e-06	3.57e-04
A_55_P1979575	Shroom2	Mus musculus shroom family member 2 (Shroom2), mRNA [NM_172441]	-1.24	2.24e-06	3.57e-04
A_55_P1956130	LOC68395	PREDICTED: Mus musculus RIKEN cDNA 0610037M15 gene, transcript variant 2 (0610037M15Rik), mRNA [XM_903697]	2.30	2.24e-06	3.57e-04
A_51_P161354	Sesn2	Mus musculus sestrin 2 (Sesn2), mRNA [NM_144907]	1.34	2.25e-06	3.57e-04
A_51_P134812	Chac1	Mus musculus ChaC, cation transport regulator-like 1 (E. coli) (Chac1), mRNA [NM_026929]	3.98	2.23e-06	3.57e-04
A_66_P138915	Fyn	Mus musculus Fyn proto-oncogene (Fyn), transcript variant 1, mRNA [NM_001122893]	1.63	2.32e-06	3.65e-04
A_51_P436878	Sertad1	Mus musculus SERTA domain containing 1 (Sertad1), mRNA [NM_018820]	2.02	2.37e-06	3.69e-04
A_55_P2063266	Piga	Mus musculus phosphatidylinositol glycan anchor biosynthesis, class A (Piga), mRNA [NM_011081]	-1.72	2.38e-06	3.69e-04
A_66_P127969	Bcat1	Mus musculus branched chain aminotransferase 1, cytosolic (Bcat1), transcript variant 2, mRNA [NM_007532]	1.47	2.40e-06	3.70e-04
A_55_P1987839	Erbb2ip	Mus musculus Erbb2 interacting protein (Erbb2ip), transcript variant 1, mRNA [NM_001005868]	-1.28	2.44e-06	3.72e-04
A_51_P323620	Thyn1	Mus musculus thymocyte nuclear protein 1 (Thyn1), mRNA [NM_144543]	1.09	2.44e-06	3.72e-04
A_55_P1960351	Cntn1	Mus musculus contactin 1 (Cntn1), transcript variant 1, mRNA [NM_001159647]	1.33	2.51e-06	3.80e-04
A_55_P1983209	Rcbtb1	Mus musculus regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1 (Rcbtb1), mRNA [NM_027764]	-1.34	2.52e-06	3.80e-04
A_55_P2043122	Arsg	Mus musculus arylsulfatase G (Arsg), transcript variant 1, mRNA [NM_028710]	-0.95	2.52e-06	3.80e-04
A_55_P1970033	Per1	Mus musculus period homolog 1 (Drosophila) (Per1), transcript variant 1, mRNA [NM_011065]	2.21	2.56e-06	3.84e-04
A_55_P2121352	Cdk5	Mus musculus cyclin-dependent kinase 5 (Cdk5), mRNA [NM_007668]	-2.21	2.57e-06	3.84e-04
A_51_P242166	Lap3	Mus musculus leucine aminopeptidase 3 (Lap3), mRNA [NM_024434]	-1.06	2.60e-06	3.86e-04
A_55_P1995173	Odc1	Mus musculus ornithine decarboxylase, structural 1 (Odc1), mRNA [NM_013614]	1.65	2.65e-06	3.91e-04
A_55_P2096395	Cdc42bpa	Mus musculus CDC42 binding protein kinase alpha (Cdc42bpa), mRNA [NM_001033285]	-1.27	2.70e-06	3.98e-04
A_55_P2149942	Ninj2	Mus musculus ninjurin 2 (Ninj2), mRNA [NM_016718]	-2.65	2.73e-06	4.00e-04
A_51_P494675	Cotl1	Mus musculus coactosin-like 1 (Dictyostelium) (Cotl1), mRNA [NM_028071]	2.14	2.75e-06	4.00e-04
A_55_P2146520	Atpgd1	Mus musculus ATP-grasp domain containing 1 (Atpgd1), mRNA [NM_134148]	-3.23	2.80e-06	4.04e-04
A_51_P430900	Dusp1	Mus musculus dual specificity phosphatase 1 (Dusp1), mRNA [NM_013642]	1.81	2.80e-06	4.04e-04
A_55_P2108837	Tuba1c	Mus musculus tubulin, alpha 1C (Tuba1c), mRNA [NM_009448]	2.25	2.85e-06	4.07e-04
A_55_P1969276	Hhip	Mus musculus Hedgehog-interacting protein (Hhip), mRNA [NM_020259]	-1.39	2.84e-06	4.07e-04
A_55_P1962771	Cyfip2	Mus musculus cytoplasmic FMR1 interacting protein 2 (Cyfip2), mRNA [NM_133769]	1.48	2.87e-06	4.08e-04
A_55_P2154387	Bmp4	Mus musculus bone morphogenetic protein 4 (Bmp4), mRNA [NM_007554]	2.32	2.88e-06	4.08e-04
A_51_P348397	Hexim1	Mus musculus hexamethylene bis-acetamide inducible 1 (Hexim1), mRNA [NM_138753]	1.55	2.94e-06	4.13e-04

A_55_P2070347	Rps2	Mus musculus ribosomal protein S2 (Rps2), mRNA [NM_008503]	0.96	3.02e-06	4.22e-04
A_55_P2139027	Plec1	Mus musculus plectin 1 (Plec1), transcript variant 13, mRNA [NM_001163540]	2.19	3.09e-06	4.26e-04
A_52_P184149	Mthfd2	Mus musculus methylenetetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase (Mthfd2), nuclear gene encoding mitochondrial protein, mRNA [NM_008638]	1.50	3.07e-06	4.26e-04
A_51_P184728	Cnksr3	Mus musculus Cnksr family member 3 (Cnksr3), mRNA [NM_172546]	1.79	3.10e-06	4.26e-04
A_55_P2111855	Gale	Mus musculus galactose-4-epimerase, UDP (Gale), mRNA [NM_178389]	1.37	3.09e-06	4.26e-04
A_55_P2032558	Gm7159	PREDICTED: Mus musculus predicted gene, EG635497 (EG635497), misc RNA [XR_002030]	1.19	3.13e-06	4.26e-04
A_55_P1987730	5730469M10Rik	Mus musculus RIKEN cDNA 5730469M10 gene (5730469M10Rik), mRNA [NM_027464]	-1.59	3.13e-06	4.26e-04
A_55_P1999349	Nudt4	Mus musculus nudix (nucleoside diphosphate linked moiety X)-type motif 4 (Nudt4), mRNA [NM_027722]	-1.40	3.14e-06	4.26e-04
A_55_P2147736	Dpysl4	Mus musculus dihydropyrimidinase-like 4 (Dpysl4), mRNA [NM_011993]	2.78	3.16e-06	4.28e-04
A_55_P2135331	Evl	Mus musculus Ena-vasodilator stimulated phosphoprotein (Evl), transcript variant 1, mRNA [NM_001163394]	1.41	3.29e-06	4.41e-04
A_55_P2374381	A230001M10Rik	Mus musculus adult male hypothalamus cDNA, RIKEN full-length enriched library, clone:A230012K17 product:unclassifiable, full insert sequence. [AK038444]	-1.58	3.37e-06	4.49e-04
A_55_P2011286	Hopx	Mus musculus HOP homeobox (Hopx), transcript variant 1, mRNA [NM_175606]	-1.64	3.41e-06	4.51e-04
A_55_P2110713	Anxa2	Mus musculus annexin A2 (Anxa2), mRNA [NM_007585]	2.48	3.40e-06	4.51e-04
A_51_P279712	Rell1	Mus musculus RELT-like 1 (Rell1), mRNA [NM_145923]	1.24	3.44e-06	4.53e-04
A_55_P2023727	Limch1	Mus musculus LIM and calponin homology domains 1 (Limch1), mRNA [NM_001001980]	-1.36	3.50e-06	4.55e-04
A_55_P2123502	Jam2	Mus musculus junction adhesion molecule 2 (Jam2), mRNA [NM_023844]	1.41	3.49e-06	4.55e-04
A_66_P133413	Gm4892	PREDICTED: Mus musculus similar to QM protein (LOC638133), mRNA [XM_914040]	0.78	3.54e-06	4.59e-04
A_51_P473229	Zbtb7b	Mus musculus zinc finger and BTB domain containing 7B (Zbtb7b), mRNA [NM_009565]	1.24	3.57e-06	4.61e-04
A_55_P1984655	Smtnl2	Mus musculus smoothelin-like 2 (Smtnl2), mRNA [NM_177776]	-2.17	3.59e-06	4.61e-04
A_55_P2032727	Gm8432	PREDICTED: Mus musculus predicted gene, EG667040 (EG667040), misc RNA [XR_001962]	1.62	3.65e-06	4.68e-04
A_51_P321886	Cmtm3	Mus musculus CKLF-like MARVEL transmembrane domain containing 3 (Cmtm3), mRNA [NM_024217]	1.64	3.67e-06	4.68e-04
A_55_P1954221	Emp1	Mus musculus epithelial membrane protein 1 (Emp1), mRNA [NM_010128]	3.45	3.68e-06	4.68e-04
A_55_P2111416	LOC100047340	PREDICTED: Mus musculus hypothetical protein LOC100047340 (LOC100047340), mRNA [XM_001477942]	1.77	3.74e-06	4.68e-04
A_66_P135173	9630013A20Rik	Mus musculus RIKEN cDNA 9630013A20 gene (9630013A20Rik), non-coding RNA [NR_015539]	2.60	3.74e-06	4.68e-04
A_51_P438805	Txnip	Mus musculus thioredoxin interacting protein (Txnip), transcript variant 1, mRNA [NM_001009935]	1.58	3.71e-06	4.68e-04
A_55_P2090880	Stk40	Mus musculus serine/threonine kinase 40 (Stk40), transcript variant 1, mRNA [NM_001145827]	1.56	3.74e-06	4.68e-04
A_51_P265869	Hspa9	Mus musculus heat shock protein 9 (Hspa9), nuclear gene encoding mitochondrial protein, mRNA [NM_010481]	1.05	3.77e-06	4.70e-04
A_51_P173709	Gprc5b	Mus musculus G protein-coupled receptor, family C, group 5, member B (Gprc5b), mRNA [NM_022420]	-0.97	3.80e-06	4.72e-04
A_55_P1979252	Glod4	Mus musculus glyoxalase domain containing 4 (Glod4),	-1.23	3.83e-06	4.73e-04

		mRNA [NM_026029]			
A_51_P480233	Nmral1	Mus musculus NmrA-like family domain containing 1 (Nmral1), mRNA [NM_026393]	-1.65	3.85e-06	4.73e-04
A_55_P2139992	Mrps18b	Mus musculus mitochondrial ribosomal protein S18B (Mrps18b), nuclear gene encoding mitochondrial protein, mRNA [NM_025878]	1.24	3.85e-06	4.73e-04
A_51_P486543	Grm3	Mus musculus glutamate receptor, metabotropic 3 (Grm3), mRNA [NM_181850]	-1.79	3.87e-06	4.73e-04
A_51_P159453	Serpina3n	Mus musculus serine (or cysteine) peptidase inhibitor, clade A, member 3N (Serpina3n), mRNA [NM_009252]	2.30	3.90e-06	4.74e-04
A_55_P2109263	Ppp1r14b	Mus musculus protein phosphatase 1, regulatory (inhibitor) subunit 14B (Ppp1r14b), mRNA [NM_008889]	1.74	3.91e-06	4.74e-04
A_55_P2069251	Prr18	Mus musculus proline rich region 18 (Prr18), transcript variant 1, mRNA [NM_178774]	-1.02	3.95e-06	4.75e-04
A_55_P2000062	Irf1	Mus musculus interferon regulatory factor 1 (Irf1), transcript variant 1, mRNA [NM_008390]	1.82	3.98e-06	4.77e-04
A_51_P368591	Tle6	Mus musculus transducin-like enhancer of split 6, homolog of Drosophila E(spl) (Tle6), mRNA [NM_053254]	1.45	3.99e-06	4.77e-04
A_51_P259571	Angptl6	Mus musculus angiopoietin-like 6 (Angptl6), mRNA [NM_145154]	1.76	4.09e-06	4.86e-04
A_51_P281089	S100a6	Mus musculus S100 calcium binding protein A6 (calcyclin) (S100a6), mRNA [NM_011313]	2.33	4.11e-06	4.87e-04
A_55_P2171116	Lgals3	Mus musculus lectin, galactose binding, soluble 3 (Lgals3), transcript variant 1, mRNA [NM_001145953]	2.76	4.16e-06	4.90e-04
A_51_P487228	B9d2	Mus musculus B9 protein domain 2 (B9d2), mRNA [NM_172148]	1.27	4.24e-06	4.96e-04
A_51_P203878	Dynll2	Mus musculus dynein light chain LC8-type 2 (Dynll2), transcript variant 1, mRNA [NM_026556]	1.28	4.29e-06	4.98e-04
A_51_P200667	Clmn	Mus musculus calmin (Clmn), transcript variant 1, mRNA [NM_053155]	-1.73	4.32e-06	4.99e-04
A_52_P540434	Ppp1cc	Mus musculus protein phosphatase 1, catalytic subunit, gamma isoform (Ppp1cc), mRNA [NM_013636]	-3.30	4.33e-06	4.99e-04
A_51_P498257	Rnf141	RING finger protein 141 (Zinc finger protein 230) [Source:UniProtKB/Swiss-Prot;Acc:Q99MB7] [ENSMUST00000106682]	-1.11	4.49e-06	5.15e-04
A_55_P2032258	Pdlim1	Mus musculus PDZ and LIM domain 1 (elfin) (Pdlim1), mRNA [NM_016861]	-1.46	4.55e-06	5.20e-04
A_55_P2144931	Gm5100	PREDICTED: Mus musculus predicted gene, EG329126 (EG329126), misc RNA [XR_001880]	1.13	4.62e-06	5.27e-04
A_52_P202142	Sv2a	Mus musculus synaptic vesicle glycoprotein 2 a (Sv2a), mRNA [NM_022030]	-1.37	4.67e-06	5.29e-04
A_55_P2060158	Ermn	Mus musculus ermin, ERM-like protein (Ermn), mRNA [NM_029972]	-1.39	4.70e-06	5.29e-04
A_55_P2106351	LOC100047749	PREDICTED: Mus musculus similar to cAMP-specific cyclic nucleotide phosphodiesterase PDE8; MMPDE8 (LOC100047749), mRNA [XM_001478817]	-1.25	4.70e-06	5.29e-04
A_55_P2086949	Cntf	Mus musculus ciliary neurotrophic factor (Cntf), mRNA [NM_170786]	1.69	4.74e-06	5.29e-04
A_55_P2065239	Gm11230	PREDICTED: Mus musculus similar to ribosomal protein (LOC100039979), mRNA [XM_001474183]	1.22	4.76e-06	5.29e-04
A_55_P2047962	Gjc2	Mus musculus gap junction protein, gamma 2 (Gjc2), transcript variant 2, mRNA [NM_175452]	-1.80	4.77e-06	5.29e-04
A_55_P2081123	Srcin1	Mus musculus SRC kinase signaling inhibitor 1 (Srcin1), mRNA [NM_018873]	-1.69	4.99e-06	5.52e-04
A_66_P100853	RP23-480B19.10	PREDICTED: Mus musculus similar to histone 2a, transcript variant 2 (Rp23-480b19.10), mRNA [XM_978341]	2.48	5.05e-06	5.56e-04
A_51_P348433	Rasal1	Mus musculus RAS protein activator like 1 (GAP1 like) (Rasal1), mRNA [NM_013832]	-2.13	5.37e-06	5.83e-04

A_55_P2035590	Gm4838	PREDICTED: Mus musculus predicted gene, EG225416 (EG225416), mRNA [XM_140295]	1.57	5.36e-06	5.83e-04
A_52_P31543	Btg2	Mus musculus B-cell translocation gene 2, anti-proliferative (Btg2), mRNA [NM_007570]	1.55	5.36e-06	5.83e-04
A_55_P2181508	Gm10653	Mus musculus predicted gene 10653 (Gm10653), non-coding RNA [NR_003965]	0.97	5.40e-06	5.83e-04
A_55_P1990919	Sepx1	Mus musculus selenoprotein X 1 (Sepx1), mRNA [NM_013759]	-1.07	5.42e-06	5.83e-04
A_55_P2095266	Gm7204	PREDICTED: Mus musculus predicted gene, EG637273, transcript variant 1 (EG637273), mRNA [XM_917437]	-1.36	5.48e-06	5.86e-04
A_55_P1972322	Btg3	Mus musculus B-cell translocation gene 3 (Btg3), mRNA [NM_009770]	1.46	5.49e-06	5.86e-04
A_55_P2141084	Odz4	Mus musculus odd Oz/ten-m homolog 4 (Drosophila) (Odz4), mRNA [NM_011858]	1.68	5.60e-06	5.97e-04
A_55_P2039284	Hspb1	Mus musculus heat shock protein 1 (Hspb1), mRNA [NM_013560]	1.62	5.66e-06	5.99e-04
A_55_P1954393	Susd4	Mus musculus sushi domain containing 4 (Susd4), mRNA [NM_144796]	1.92	5.67e-06	5.99e-04
A_55_P2095688	Sh3bp5l	Mus musculus SH3 binding domain protein 5 like (Sh3bp5l), transcript variant 1, mRNA [NM_001161338]	-1.01	5.72e-06	6.03e-04
A_51_P209372	Sc4mol	Mus musculus sterol-C4-methyl oxidase-like (Sc4mol), mRNA [NM_025436]	-1.43	5.78e-06	6.07e-04
A_55_P2042356	Rftn1	Mus musculus raftlin lipid raft linker 1 (Rftn1), mRNA [NM_181397]	-2.10	5.85e-06	6.12e-04
A_55_P2005691	Gm8420	PREDICTED: Mus musculus similar to ribosomal protein L15 (LOC667014), mRNA [XM_001473655]	0.97	5.89e-06	6.15e-04
A_51_P367060	Ifrd1	Mus musculus interferon-related developmental regulator 1 (Ifrd1), mRNA [NM_013562]	1.19	6.06e-06	6.29e-04
A_51_P368496	Tmem98	Mus musculus transmembrane protein 98 (Tmem98), mRNA [NM_029537]	-1.44	6.07e-06	6.29e-04
A_55_P2098471	Rps19	Mus musculus ribosomal protein S19 (Rps19), mRNA [NM_023133]	1.62	6.12e-06	6.31e-04
A_55_P2044582	Iglon5	Mus musculus IgLON family member 5 (Iglon5), mRNA [NM_001164518]	2.01	6.39e-06	6.53e-04
A_55_P1997604	Pla2g4a	Mus musculus phospholipase A2, group IVA (cytosolic, calcium-dependent) (Pla2g4a), mRNA [NM_008869]	-1.28	6.40e-06	6.53e-04
A_52_P167278	Mthfd1l	Mus musculus methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like (Mthfd1l), nuclear gene encoding mitochondrial protein, transcript variant 2, mRNA [NM_172308]	1.39	6.43e-06	6.54e-04
A_51_P277336	Sdpr	Mus musculus serum deprivation response (Sdpr), mRNA [NM_138741]	-1.31	6.45e-06	6.54e-04
A_55_P1990210	Scpep1	Mus musculus serine carboxypeptidase 1 (Scpep1), mRNA [NM_029023]	1.41	6.53e-06	6.60e-04
A_55_P2106916	Kcna1	Mus musculus potassium voltage-gated channel, shaker-related subfamily, member 1 (Kcna1), mRNA [NM_010595]	-1.39	6.67e-06	6.72e-04
A_55_P2131954	Gm2590	PREDICTED: Mus musculus hypothetical protein LOC100040086 (LOC100040086), mRNA [XM_001474060]	-2.04	6.69e-06	6.72e-04
A_55_P2024888	Ctss	Mus musculus cathepsin S (Ctss), mRNA [NM_021281]	2.84	6.84e-06	6.85e-04
A_51_P461779	Ppp2r2c	Mus musculus protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), gamma isoform (Ppp2r2c), mRNA [NM_172994]	-1.54	6.91e-06	6.90e-04
A_55_P2150555	Pcgf5	Mus musculus polycomb group ring finger 5 (Pcgf5), mRNA [NM_029508]	1.47	6.96e-06	6.93e-04
A_55_P2123002	Tet1	Mus musculus tet oncogene 1 (Tet1), mRNA [NM_027384]	-1.55	7.00e-06	6.95e-04
A_51_P472829	Aif1l	Mus musculus allograft inflammatory factor 1-like (Aif1l), mRNA [NM_145144]	-1.42	7.03e-06	6.96e-04
A_52_P594768	Aprt	Mus musculus adenine phosphoribosyl transferase (Aprt),	1.65	7.15e-06	7.05e-04

		mRNA [NM_009698]			
A_55_P2059931	Prom1	Mus musculus prominin 1 (Prom1), transcript variant 2, mRNA [NM_001163577]	2.02	7.21e-06	7.09e-04
A_51_P226269	1190002H23Rik	Mus musculus RIKEN cDNA 1190002H23 gene (1190002H23Rik), mRNA [NM_025427]	1.99	7.28e-06	7.13e-04
A_51_P285077	Hhatl	Mus musculus hedgehog acyltransferase-like (Hhatl), transcript variant 1, mRNA [NM_029095]	-2.17	7.46e-06	7.29e-04
A_55_P1989061	Tsc22d3	Mus musculus TSC22 domain family, member 3 (Tsc22d3), transcript variant 1, mRNA [NM_001077364]	-1.56	7.73e-06	7.53e-04
A_66_P106113	Rhoj	Mus musculus ras homolog gene family, member J (Rhoj), mRNA [NM_023275]	1.39	7.77e-06	7.54e-04
A_55_P1978506	H2-Q6	Mus musculus histocompatibility 2, Q region locus 6 (H2-Q6), mRNA [NM_207648]	2.19	7.79e-06	7.54e-04
A_55_P1968295	Pacsin3	Mus musculus protein kinase C and casein kinase substrate in neurons 3 (Pacsin3), mRNA [NM_028733]	-1.67	7.91e-06	7.61e-04
A_55_P2025538	Ano4	Mus musculus anoctamin 4 (Ano4), mRNA [NM_178773]	-1.34	7.93e-06	7.61e-04
A_51_P432460	Ppp1r14a	Mus musculus protein phosphatase 1, regulatory (inhibitor) subunit 14A (Ppp1r14a), mRNA [NM_026731]	-1.34	8.14e-06	7.73e-04
A_55_P2101906	Rpl10a	Mus musculus ribosomal protein L10A (Rpl10a), mRNA [NM_011287]	0.94	8.16e-06	7.73e-04
A_55_P2033282	Cept1	Mus musculus choline/ethanolaminephosphotransferase 1 (Cept1), mRNA [NM_133869]	-0.91	8.18e-06	7.73e-04
A_55_P2094520	Fam171a1	Mus musculus family with sequence similarity 171, member A1 (Fam171a1), mRNA [NM_001081161]	-1.28	8.39e-06	7.87e-04
A_51_P209150	Pcdh10	Mus musculus protocadherin 10 (Pcdh10), transcript variant 2, mRNA [NM_001098172]	1.31	8.40e-06	7.87e-04
A_52_P243391	Sema4f	Mus musculus sema domain, immunoglobulin domain (Ig), TM domain, and short cytoplasmic domain (Sema4f), transcript variant 1, mRNA [NM_011350]	1.42	8.45e-06	7.90e-04
A_55_P1974957	Tnr	Mus musculus tenascin R (Tnr), mRNA [NM_022312]	1.96	8.59e-06	7.98e-04
A_55_P2124498	Il17rb	Mus musculus interleukin 17 receptor B (Il17rb), mRNA [NM_019583]	-1.48	8.67e-06	7.99e-04
A_51_P246166	Expi	Mus musculus extracellular proteinase inhibitor (Expi), mRNA [NM_007969]	-2.55	8.63e-06	7.99e-04
A_55_P2036280	Psen2	Mus musculus presenilin 2 (Psen2), transcript variant 2, mRNA [NM_001128605]	-1.22	8.69e-06	7.99e-04
A_55_P2147427	Prdx1	Mus musculus peroxiredoxin 1 (Prdx1), mRNA [NM_011034]	-1.41	8.72e-06	7.99e-04
A_51_P250058	Epas1	Mus musculus endothelial PAS domain protein 1 (Epas1), mRNA [NM_010137]	-1.16	8.73e-06	7.99e-04
A_66_P122087	Zfp622	Mus musculus zinc finger protein 622 (Zfp622), mRNA [NM_144523]	0.99	8.81e-06	8.04e-04
A_55_P2135631	Rps18	Mus musculus ribosomal protein S18 (Rps18), mRNA [NM_011296]	1.22	8.91e-06	8.11e-04
A_55_P1963529	Abcb10	Mus musculus ATP-binding cassette, sub-family B (MDR/TAP), member 10 (Abcb10), nuclear gene encoding mitochondrial protein, mRNA [NM_019552]	-1.25	8.93e-06	8.11e-04
A_55_P2181341	Ecel1	Mus musculus endothelin converting enzyme-like 1 (Ecel1), mRNA [NM_021306]	2.31	9.09e-06	8.15e-04
A_55_P2153292	Tubb2c	Mus musculus tubulin, beta 2C (Tubb2c), mRNA [NM_146116]	1.05	9.07e-06	8.15e-04
A_52_P163795	Tubb5	Mus musculus tubulin, beta 5 (Tubb5), mRNA [NM_011655]	1.37	9.08e-06	8.15e-04
A_55_P2027087	Plcl1	Mus musculus phospholipase C-like 1 (Plcl1), mRNA [NM_001114663]	-1.26	9.13e-06	8.15e-04
A_55_P2090070	Myh14	Mus musculus myosin, heavy polypeptide 14 (Myh14), mRNA [NM_028021]	-1.41	9.14e-06	8.15e-04
A_55_P2091736	Rassf2	Mus musculus Ras association (RalGDS/AF-6) domain family member 2 (Rassf2), mRNA [NM_175445]	-0.91	9.17e-06	8.16e-04

A_51_P418056	Sc5d	Mus musculus sterol-C5-desaturase (fungal ERG3, delta-5-desaturase) homolog (S. cerevisae) (Sc5d), mRNA [NM_172769]	-1.36	9.32e-06	8.27e-04
A_55_P2021216	Crlf3	Mus musculus cytokine receptor-like factor 3 (Crlf3), mRNA [NM_018776]	-1.56	9.54e-06	8.44e-04
A_51_P158678	Fam181b	Mus musculus family with sequence similarity 181, member B (Fam181b), mRNA [NM_021427]	3.79	9.89e-06	8.70e-04
A_55_P2005552	Arhgef10l	Mus musculus Rho guanine nucleotide exchange factor (GEF) 10-like (Arhgef10l), transcript variant 1, mRNA [NM_172415]	1.95	1.01e-05	8.82e-04
A_55_P2064876	Mtvr2	Mus musculus mammary tumor virus receptor 2 (Mtvr2), transcript variant 1, mRNA [NM_181452]	1.23	1.01e-05	8.82e-04
A_55_P1985890	Tiparp	Mus musculus TCDD-inducible poly(ADP-ribose) polymerase (Tiparp), mRNA [NM_178892]	1.21	1.02e-05	8.87e-04
A_52_P88983	Dock5	Mus musculus dedicator of cytokinesis 5 (Dock5), mRNA [NM_177780]	-1.89	1.04e-05	9.01e-04
A_55_P1969745	Pitpnm1	Mus musculus phosphatidylinositol transfer protein, membrane-associated 1 (Pitpnm1), transcript variant 2, mRNA [NM_001136078]	1.47	1.05e-05	9.07e-04
A_55_P2030859	Gm8225	PREDICTED: Mus musculus predicted gene, EG666668 (EG666668), mRNA [XM_985281]	1.05	1.05e-05	9.08e-04
A_51_P155313	Gsto1	Mus musculus glutathione S-transferase omega 1 (Gsto1), mRNA [NM_010362]	2.08	1.06e-05	9.10e-04
A_55_P2125743	Gm8842	PREDICTED: Mus musculus predicted gene, EG667847, transcript variant 2 (EG667847), mRNA [XM_001003664]	0.75	1.06e-05	9.10e-04
A_55_P2020128	Dhrs3	Mus musculus dehydrogenase/reductase (SDR family) member 3 (Dhrs3), mRNA [NM_011303]	1.41	1.06e-05	9.10e-04
A_51_P194306	Lrrc1	Mus musculus leucine rich repeat containing 1 (Lrrc1), transcript variant 2, mRNA [NM_172528]	-1.05	1.06e-05	9.10e-04
A_51_P498890	Degs1	Mus musculus degenerative spermatocyte homolog 1 (Drosophila) (Degs1), mRNA [NM_007853]	-0.96	1.07e-05	9.10e-04
A_55_P1960049	2810408A11Rik	Mus musculus RIKEN cDNA 2810408A11 gene (2810408A11Rik), mRNA [NM_027419]	1.35	1.07e-05	9.10e-04
A_55_P1991770	Pdlim4	Mus musculus PDZ and LIM domain 4 (Pdlim4), mRNA [NM_019417]	4.24	1.08e-05	9.12e-04
A_55_P2165314	Trio	Mus musculus triple functional domain (PTPRF interacting) (Trio), mRNA [NM_001081302]	2.17	1.09e-05	9.21e-04
A_52_P18807	Eif3c	Mus musculus eukaryotic translation initiation factor 3, subunit C (Eif3c), mRNA [NM_146200]	1.05	1.11e-05	9.31e-04
A_51_P193794	Lrp1	Mus musculus low density lipoprotein receptor-related protein 1 (Lrp1), mRNA [NM_008512]	1.57	1.14e-05	9.35e-04
A_55_P2004159	LOC100039646	PREDICTED: Mus musculus similar to polyprotein (LOC100039646), mRNA [XM_001472835]	-1.89	1.12e-05	9.35e-04
A_66_P129893	1700047M11Rik	Mus musculus RIKEN cDNA 1700047M11 gene (1700047M11Rik), non-coding RNA [NR_015458]	-1.36	1.12e-05	9.35e-04
A_55_P1984113	Nup62	Mus musculus nucleoporin 62 (Nup62), mRNA [NM_053074]	1.35	1.12e-05	9.35e-04
A_51_P108901	Ccdc86	Mus musculus coiled-coil domain containing 86 (Ccdc86), mRNA [NM_023731]	1.34	1.13e-05	9.35e-04
A_55_P2009285	Fbxo25	Mus musculus F-box protein 25 (Fbxo25), mRNA [NM_025785]	-1.13	1.13e-05	9.35e-04
A_55_P2028961	Idi1	Mus musculus isopentenyl-diphosphate delta isomerase (Idi1), mRNA [NM_145360]	-1.66	1.14e-05	9.35e-04
A_55_P2005190	Herc4	Mus musculus hect domain and RLD 4 (Herc4), mRNA [NM_026101]	-1.45	1.14e-05	9.35e-04
A_55_P2151609	Sorl1	Mus musculus sortilin-related receptor, LDLR class A repeats-containing (Sorl1), mRNA [NM_011436]	-1.54	1.15e-05	9.35e-04
A_51_P144349	Dtx4	Mus musculus deltex 4 homolog (Drosophila) (Dtx4), mRNA [NM_172442]	1.16	1.15e-05	9.35e-04

A_52_P284889	Prkcz	Mus musculus protein kinase C, zeta (Prkcz), transcript variant 1, mRNA [NM_008860]	-1.26	1.15e-05	9.39e-04
A_51_P237668	Bex2	Mus musculus brain expressed X-linked 2 (Bex2), mRNA [NM_009749]	1.76	1.18e-05	9.56e-04
A_51_P173961	Pdrg1	Mus musculus p53 and DNA damage regulated 1 (Pdrg1), mRNA [NM_178939]	0.90	1.18e-05	9.56e-04
A_55_P2001718	Pex1	Mus musculus peroxisomal biogenesis factor 1 (Pex1), mRNA [NM_027777]	-1.24	1.19e-05	9.62e-04
A_51_P505493	Elovl5	Mus musculus ELOVL family member 5, elongation of long chain fatty acids (yeast) (Elovl5), mRNA [NM_134255]	-0.98	1.20e-05	9.69e-04
A_55_P2022074	Klf10	Mus musculus Kruppel-like factor 10 (Klf10), mRNA [NM_013692]	1.57	1.23e-05	9.86e-04
A_55_P2052696	Synm	Mus musculus synemin, intermediate filament protein (Synm), transcript variant 1, mRNA [NM_201639]	-1.42	1.23e-05	9.86e-04
A_51_P234113	Nod1	Mus musculus nucleotide-binding oligomerization domain containing 1 (Nod1), mRNA [NM_172729]	-1.35	1.23e-05	9.86e-04
A_51_P341918	Tsc22d1	Mus musculus TSC22 domain family, member 1 (Tsc22d1), transcript variant 2, mRNA [NM_009366]	1.51	1.26e-05	9.96e-04
A_55_P2037524	Rps15	Mus musculus ribosomal protein S15 (Rps15), mRNA [NM_009091]	0.91	1.26e-05	9.96e-04
A_55_P2020577	Pcolce	Mus musculus procollagen C-endopeptidase enhancer protein (Pcolce), mRNA [NM_008788]	1.33	1.26e-05	9.96e-04
A_51_P195958	Phlda1	Mus musculus pleckstrin homology-like domain, family A, member 1 (Phlda1), mRNA [NM_009344]	1.12	1.26e-05	9.96e-04

Table 4.4. Common DEGs identified in the *corpus callosum* and OPC analysis.

Symbol	**Gene name**
Gdf15	growth differentiation factor 15
Pigz	phosphatidylinositol glycan anchor biosynthesis, class Z
Trib3	tribbles pseudokinase 3
Ninj2	ninjurin 2
Ccng1	cyclin G1
Slc34a3	solute carrier family 34 (sodium phosphate), member 3
Atf5	activating transcription factor 5
Xrcc3	X-ray repair complementing defective repair in Chinese hamster cells 3
Ddit3	DNA-damage inducible transcript 3
Moxd1	monooxygenase, DBH-like 1
Smtnl2	smoothelin-like 2
Ppp1r14a	protein phosphatase 1, regulatory inhibitor subunit 14A
Sesn2	sestrin 2
Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)
Tmem125	transmembrane protein 125
Tmprss5	transmembrane protease, serine 5 (spinesin)
Slc7a5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5
Klf4	Kruppel-like factor 4 (gut)
Eif4ebp1	eukaryotic translation initiation factor 4E binding protein 1
Slc3a2	solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2
Arap2	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 2

Gzmm	granzyme M (lymphocyte met-ase 1)
Sgk2	serum/glucocorticoid regulated kinase 2
Bbc3	BCL2 binding component 3
Nes	nestin
Gas5	growth arrest specific 5
Fdps	farnesyl diphosphate synthetase
Prima1	proline rich membrane anchor 1
Serpinb1a	serine (or cysteine) peptidase inhibitor, clade B, member 1a
Ldlr	low density lipoprotein receptor
Gjc2	gap junction protein, gamma 2
Ephx1	epoxide hydrolase 1, microsomal
Ephx1	epoxide hydrolase 1, microsomal
B230206H07Rik	RIKEN cDNA B230206H07 gene
Hmgcs1	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1
Galnt6	polypeptide N-acetylgalactosaminyltransferase 6
Galnt6	polypeptide N-acetylgalactosaminyltransferase 6
Nupr1	nuclear protein transcription regulator 1
Adamts1	a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 1
Pcyt2	phosphate cytidylyltransferase 2, ethanolamine
Gadd45b	growth arrest and DNA-damage-inducible 45 beta
Nacad	NAC alpha domain containing
Klk6	kallikrein related-peptidase 6
Tmeff1	transmembrane protein with EGF-like and two follistatin-like domains 1
Mog	myelin oligodendrocyte glycoprotein
Aen	apoptosis enhancing nuclease
Nmral1	NmrA-like family domain containing 1
Rftn1	raftlin lipid raft linker 1
Eprs	glutamyl-prolyl-tRNA synthetase
Nkain1	Na+/K+ transporting ATPase interacting 1
Fzd1	frizzled class receptor 1
Rps27l	ribosomal protein S27-like
Rhog	ras homolog family member G
Arrdc4	arrestin domain containing 4
Opalin	oligodendrocytic myelin paranodal and inner loop protein
Anln	anillin, actin binding protein
Sytl2	synaptotagmin-like 2
Ccl2	chemokine (C-C motif) ligand 2
Gadd45a	growth arrest and DNA-damage-inducible 45 alpha
Prr18	proline rich 18
Synj2	synaptojanin 2
Ifrd1	interferon-related developmental regulator 1
Adssl1	adenylosuccinate synthetase like 1
Kctd15	potassium channel tetramerisation domain containing 15
Ppp1r15a	protein phosphatase 1, regulatory subunit 15A

Gal3st1	galactose-3-O-sulfotransferase 1
Maff	v-maf musculoaponeurotic fibrosarcoma oncogene family, protein F (avian)
Cntn2	contactin 2
Nipal4	NIPA-like domain containing 4
Cdk18	cyclin-dependent kinase 18
Mgp	matrix Gla protein
Ptprd	protein tyrosine phosphatase, receptor type, D
Lgi3	leucine-rich repeat LGI family, member 3
Tor3a	torsin family 3, member A
Mcam	melanoma cell adhesion molecule
Fah	fumarylacetoacetate hydrolase
Rgs3	regulator of G-protein signaling 3
Nfil3	nuclear factor, interleukin 3, regulated
Mbp	myelin basic protein
Dhcr7	7-dehydrocholesterol reductase
Ano4	anoctamin 4
Cyb5r2	cytochrome b5 reductase 2
Plekhh1	pleckstrin homology domain containing, family H (with MyTH4 domain) member 1
Ttll7	tubulin tyrosine ligase-like family, member 7
Runx1	runt related transcription factor 1
Odc1	ornithine decarboxylase, structural 1
Adamtsl4	ADAMTS-like 4
Gamt	guanidinoacetate methyltransferase
Rasgrp3	RAS, guanyl releasing protein 3
Cebpg	CCAAT/enhancer binding protein (C/EBP), gamma
1110038B12Rik	RIKEN cDNA 1110038B12 gene
Cebpb	CCAAT/enhancer binding protein (C/EBP), beta
Abca2	ATP-binding cassette, sub-family A (ABC1), member 2
Omg	oligodendrocyte myelin glycoprotein
Tppp	tubulin polymerization promoting protein
Mast4	microtubule associated serine/threonine kinase family member 4
Rasl12	RAS-like, family 12

Table 4.5. Potential ligands in microglia that could affect gene expression after cuprizone treatment in OPCs ordered by the Pearson correlation coefficient.

	Ligand		**Ligand**		**Ligand**
1	TFPI	16	SERPINE1	32	FN1
2	SEMA4D	17	PROS1	33	BMP2
3	GSTP1	18	GAS6	34	PLAU
4	SERPINE2	19	ADAM9	35	SPP1

5	LRPAP1	20	DUSP18	36	LRRC4B
6	THBS1	21	JAM2	37	VEGFA
7	HSP90B1	22	CORT	38	OSM
8	EFNB2	23	VCAM1	39	IFNA5
9	F11R	24	ADAM15	40	IHH
10	C3	25	PTPRC	41	IL6
11	EFNB1	26	COL2A1	42	APOE
12	PF4	27	CSF1	43	IL15
13	RGMA	28	PSAP	44	NPNT
14	LIPH	29	CLCF1	45	TNF
15	ARF1	30	TNFSF9	46	IGF1
		31	ADAM17	47	CADM1

Table 4.6. Mean expression of microglia ligands and adjusted p-value of differential expression in microglia from cuprizone treated and control mice.

Ligand	Name	Mean expression in microglia from control mice	Mean expression in microglia from cuprizone treated mice	Fold change	Adjusted p-value
PLAU	Secreted phosphoprotein 1	8.69	9.67	1.94	0.052
SPP1	Plasminogen activator, urokinase	5.06	9.84	1.11	0.052

Table 4.7. Mean expression of OPC target genes and adjusted p-value of differential expression in OPCs from cuprizone treated and control mice.

Target	Name	Mean expression in OPCs from control mice	Mean expression in OPCs from cuprizone treated mice	Fold change	Adjusted p-value
Gadd45b	growth arrest and DNA-damage-inducible 45 beta	10.84	14.51	1.34	3.32e-05
Hist1h3d		13.77	15.55	1.13	3.32e-05
Bbc3	BCL2 binding component 3	11.33	14.24	1.26	3.61e-05

Tnfrsf12a	tumor necrosis factor receptor superfamily, member 12a	9.82	13.34	1.36	7.25e-05
Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)	9.30	15.17	1.63	1.07e-04
Fosb	FBJ osteosarcoma oncogene B	11.78	14.32	1.22	1.38e-04
Abca1	ATP-binding cassette, sub-family A (ABC1), member 1	11.16	13.40	1.20	2.10e-04
Fam181b	family with sequence similarity 181, member B	8.80	12.59	1.43	2.10e-04
Vgf	VGF nerve growth factor inducible	8.98	11.80	1.31	5.08e-04
Klf4	Kruppel-like factor 4 (gut)	11.08	14.15	1.28	5.08e-04
Kdr	kinase insert domain protein receptor	10.76	8.99	0.84	5.08e-04
Gstp1	glutathione S-transferase, pi 1	15.01	14.19	0.94	6.83e-04
Hexim1	hexamethylene bis-acetamide inducible 1	10.37	11.92	1.15	7.02e-04
Trim47	tripartite motif-containing 47	10.00	12.24	1.22	7.02e-04
Egr2	early growth response 2	10.38	12.85	1.24	7.45e-04
Sgk2	serum/glucocorticoid regulated kinase 2	14.82	12.16	0.82	7.79e-04
Ccnd1	cyclin D1	9.92	13.32	1.34	8.81e-04
Il18	interleukin 18	13.55	12.34	0.91	1.00e-03
Hmga1	high mobility group AT-hook 1	12.84	15.50	1.21	1.40e-03
Ppp1r15a	protein phosphatase 1, regulatory subunit 15A	12.47	15.43	1.24	1.40e-03
Dusp1	dual specificity phosphatase 1	11.41	13.23	1.16	1.57e-03
Egr1	early growth response 1	13.21	15.70	1.19	1.57e-03
Gadd45g	growth arrest and DNA-damage-inducible 45 gamma	11.15	15.24	1.37	1.57e-03
Chpf	chondroitin polymerizing factor	11.33	12.92	1.14	1.57e-03
Rab37	RAB37, member RAS oncogene family	11.40	10.28	0.90	1.57e-03
Adamtsl4	ADAMTS-like 4	14.13	11.65	0.82	1.57e-03
Pdgfra	platelet derived growth factor receptor, alpha polypeptide	9.35	10.82	1.16	1.57e-03
Cntf	ciliary neurotrophic factor	10.32	12.01	1.16	1.57e-03
C1qc	complement component 1, q subcomponent, C chain	9.57	12.34	1.29	1.57e-03
Hmgcs1	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1	15.24	13.50	0.89	1.63e-03
Itih3	inter-alpha trypsin inhibitor, heavy chain 3	13.02	10.49	0.81	1.66e-03
Smad7	SMAD family member 7	13.14	11.94	0.91	1.75e-03
Nfil3	nuclear factor, interleukin 3, regulated	11.65	13.75	1.18	1.85e-03
Midn	midnolin	9.99	12.55	1.26	1.95e-03
Vim	vimentin	10.19	13.81	1.36	1.99e-03
Tnfrsf1a	tumor necrosis factor receptor superfamily, member 1a	9.44	11.09	1.17	2.19e-03

Nrcam	neuronal cell adhesion molecule	10.02	12.56	1.25	2.29e-03
Dhrs3	dehydrogenase/reductase (SDR family) member 3	10.19	11.60	1.14	2.60e-03
Traf4	TNF receptor associated factor 4	9.68	12.26	1.27	2.63e-03
Cdh13	cadherin 13	9.18	12.09	1.32	2.63e-03
Ldlr	low density lipoprotein receptor	12.66	11.05	0.87	2.81e-03
S100a10	S100 calcium binding protein A10 (calpactin)	9.46	12.25	1.30	2.86e-03
Pcdhga9	protocadherin gamma subfamily A, 9	10.71	11.93	1.11	2.96e-03
Klf6	Kruppel-like factor 6	12.88	14.53	1.13	3.03e-03
Atf4	activating transcription factor 4	10.68	12.04	1.13	3.03e-03
Serpind1	serine (or cysteine) peptidase inhibitor, clade D, member 1	12.36	10.60	0.86	3.10e-03
Timp3	tissue inhibitor of metalloproteinase 3	10.82	13.12	1.21	3.10e-03
Hist1h2ag		13.02	15.17	1.16	4.15e-03
Tsc22d3	TSC22 domain family, member 3	14.90	13.33	0.89	4.98e-03
Lmna	lamin A	12.29	14.20	1.16	5.01e-03
Gdf15	growth differentiation factor 15	8.91	14.19	1.59	5.01e-03
Odc1	ornithine decarboxylase, structural 1	11.01	12.66	1.15	5.01e-03
Bax	BCL2-associated X protein	13.11	14.07	1.07	5.01e-03
Rps19	ribosomal protein S19	13.44	15.06	1.12	5.01e-03
Socs3	suppressor of cytokine signaling 3	11.13	14.29	1.28	5.05e-03
Synpo	synaptopodin	12.27	11.25	0.92	5.19e-03
Klf10	Kruppel-like factor 10	10.07	11.65	1.16	6.18e-03
Ddc	dopa decarboxylase	13.71	12.80	0.93	6.18e-03
Cdk5r1	cyclin-dependent kinase 5, regulatory subunit 1 (p35)	10.93	12.01	1.10	8.98e-03
Lrp1	low density lipoprotein receptor-related protein 1	10.34	12.00	1.16	9.07e-03
Plin4	perilipin 4	11.79	13.36	1.13	9.07e-03
Ifit3	interferon-induced protein with tetratricopeptide repeats 3	9.33	11.03	1.18	9.17e-03
Myh9	myosin, heavy polypeptide 9, non-muscle	12.76	13.59	1.06	9.36e-03
Fos	FBJ osteosarcoma oncogene	12.59	14.95	1.19	9.80e-03
Ank3	ankyrin 3, epithelial	11.95	10.80	0.90	9.80e-03
Apln	apelin	12.35	11.03	0.89	9.80e-03
Per1	period circadian clock 1	12.20	14.41	1.18	1.00e-02
Tle3	transducin-like enhancer of split 3	13.65	14.54	1.07	1.00e-02
Tap2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	10.53	12.63	1.20	1.09e-02
Atf3	activating transcription factor 3	9.71	13.05	1.34	1.19e-02
Zfp36l1	zinc finger protein 36, C3H type-like 1	9.79	11.55	1.18	1.19e-02
Csrnp1	cysteine-serine-rich nuclear protein	11.70	12.93	1.11	1.19e-02

	1				
C4b	complement component 4B (Chido blood group)	13.80	15.89	1.15	1.19e-02
Cdk18	cyclin-dependent kinase 18	15.67	14.68	0.94	1.29e-02
Crybg3	beta-gamma crystallin domain containing 3	12.51	11.29	0.90	1.36e-02
Cebpb	CCAAT/enhancer binding protein (C/EBP), beta	9.61	12.35	1.28	1.41e-02
Hist1h4d		11.42	13.42	1.17	1.50e-02
Olig2	oligodendrocyte transcription factor 2	13.02	13.99	1.07	1.50e-02
Stat3	signal transducer and activator of transcription 3	12.83	13.59	1.06	1.76e-02
Sgk1	serum/glucocorticoid regulated kinase 1	13.72	15.42	1.12	1.80e-02
Nfkbia	nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha	13.02	14.38	1.10	1.83e-02
Rab34	RAB34, member RAS oncogene family	10.57	12.47	1.18	1.90e-02
Cd44	CD44 antigen	9.51	10.83	1.14	1.90e-02
Anxa2	annexin A2	11.49	14.06	1.22	1.90e-02
Col1a2	collagen, type I, alpha 2	11.44	12.73	1.11	1.94e-02
Gadd45a	growth arrest and DNA-damage-inducible 45 alpha	10.56	12.64	1.20	2.04e-02
C1qb	complement component 1, q subcomponent, beta polypeptide	9.35	11.19	1.20	2.09e-02
Tgif1	TGFB-induced factor homeobox 1	8.84	12.71	1.44	2.14e-02
Spp1	secreted phosphoprotein 1	9.26	10.42	1.13	2.23e-02
Bcl6	B cell leukemia/lymphoma 6	12.51	13.62	1.09	2.30e-02
Mfge8	milk fat globule-EGF factor 8 protein	13.48	14.49	1.07	2.48e-02
Arhgef10l	Rho guanine nucleotide exchange factor (GEF) 10-like	9.48	11.96	1.26	2.59e-02
Reep1	receptor accessory protein 1	9.76	10.99	1.13	2.59e-02
Ddit4	DNA-damage-inducible transcript 4	14.37	15.55	1.08	2.64e-02
Csf1r	colony stimulating factor 1 receptor	11.50	13.92	1.21	2.67e-02
Trib1	tribbles pseudokinase 1	8.13	11.74	1.44	2.93e-02
Tnfaip3	tumor necrosis factor, alpha-induced protein 3	8.94	11.00	1.23	2.97e-02
Cirbp	cold inducible RNA binding protein	12.46	14.16	1.14	2.97e-02
Npepps	aminopeptidase puromycin sensitive	14.04	13.24	0.94	2.97e-02
Jun	jun proto-oncogene	14.96	15.97	1.07	3.20e-02
Ly86	lymphocyte antigen 86	7.52	12.08	1.61	3.48e-02
Mgp	matrix Gla protein	12.43	14.42	1.16	3.67e-02
Malat1	metastasis associated lung adenocarcinoma transcript 1 (non-	12.95	14.16	1.09	4.04e-02

	coding RNA)				
Zeb2	zinc finger E-box binding homeobox 2	10.72	9.59	0.89	4.04e-02
Clic1	chloride intracellular channel 1	10.10	12.23	1.21	4.26e-02
Vcan	versican	8.95	11.37	1.27	4.37e-02
Magi1	membrane associated guanylate kinase, WW and PDZ domain containing 1	13.71	12.88	0.94	4.73e-02

Table 4.8. Mean expression of OPC receptors and adjusted p-value of differential expression in OPCs from cuprizone treated and control mice.

Receptor	Name	Mean expression in OPCs from control mice	Mean expression in OPCs from cuprizone treated mice	Fold change	Adjusted p-value
Jam3	junction adhesion molecule 3	15.63	14.65	0.94	5.69e-05
Plxnb2	plexin B2	11.21	12.53	1.12	4.28e-03
Hhip	Hedgehog-interacting protein	14.11	12.72	0.90	4.28e-03
Tnfrsf1a	tumor necrosis factor receptor superfamily, member 1a	9.44	11.09	1.17	6.06e-03
Acvr1	activin A receptor, type 1	12.40	13.27	1.07	6.06e-03
Ldlr	low density lipoprotein receptor	12.66	11.05	0.87	7.19e-03
Fgfr2	fibroblast growth factor receptor 2	11.40	10.09	0.89	8.94e-03
Itgb4	integrin beta 4	14.62	12.61	0.86	8.94e-03
Ephb1	Eph receptor B1	14.38	13.59	0.94	1.23e-02
Lrp1	low density lipoprotein receptor-related protein 1	10.34	12.00	1.16	2.06e-02
Lpar1	lysophosphatidic acid receptor 1	12.06	10.77	0.89	2.12e-02
Tyro3	TYRO3 protein tyrosine kinase 3	11.69	10.51	0.90	3.22e-02
Itgb5	integrin beta 5	11.37	12.11	1.07	3.22e-02
Axl	AXL receptor tyrosine kinase	9.21	11.61	1.26	4.76e-02
Sorl1	sortilin-related receptor, LDLR class A repeats-containing	13.39	11.85	0.88	4.76e-02

7.2. Figures

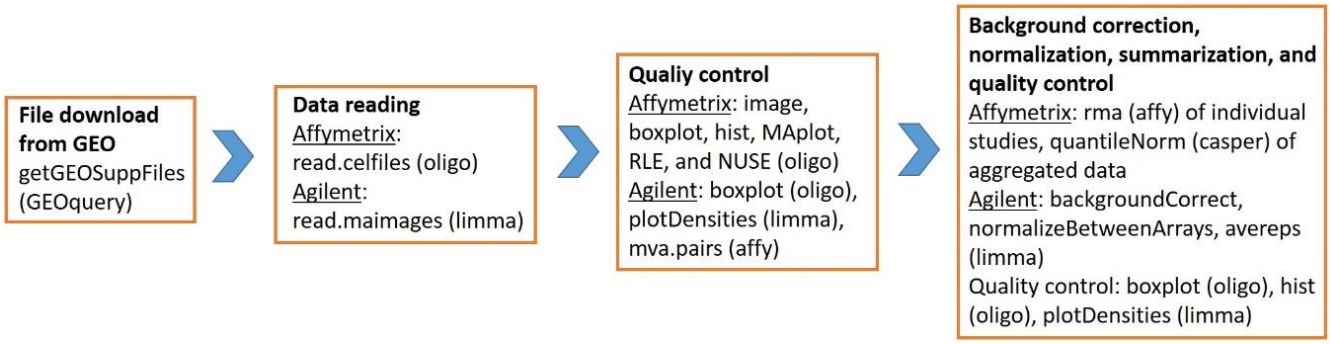


Figure 3.1. Preprocessing strategy.

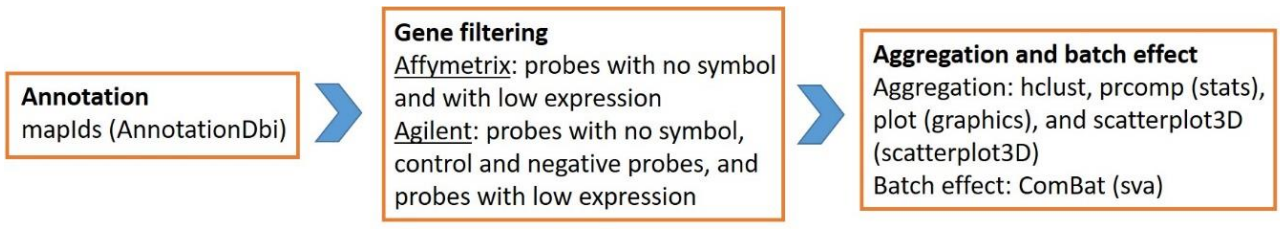


Figure 3.2. Annotation, gene filtering and aggregation strategy.

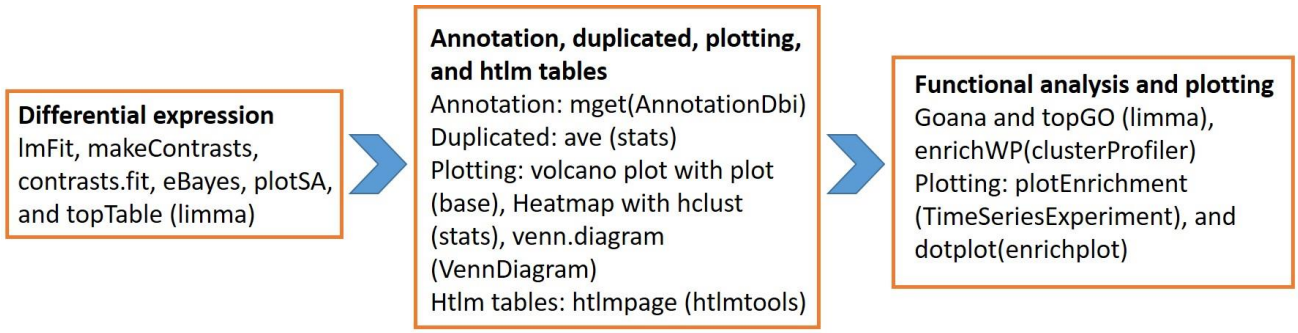


Figure 3.3. Differential expression and functional analysis strategy.

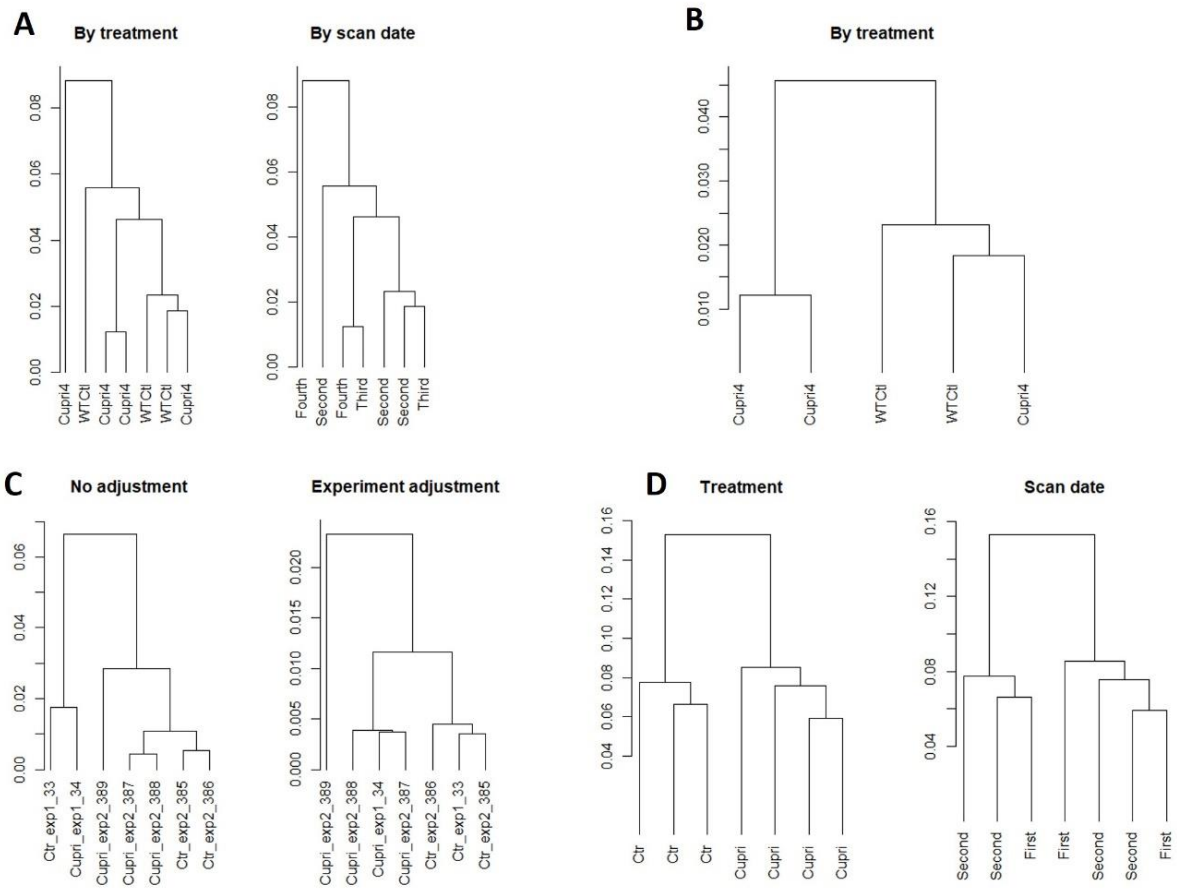


Figure 4.1. Dendrograms of the hierarchical clustering performed with the normalized and filtered expression data in the *corpus callosum* (A-B), microglia (C), and OPC analyses (D). Figure A represents the hierarchical clustering of all samples available in the *corpus callosum* study and Figure B the clustering of the samples included in the final analysis.

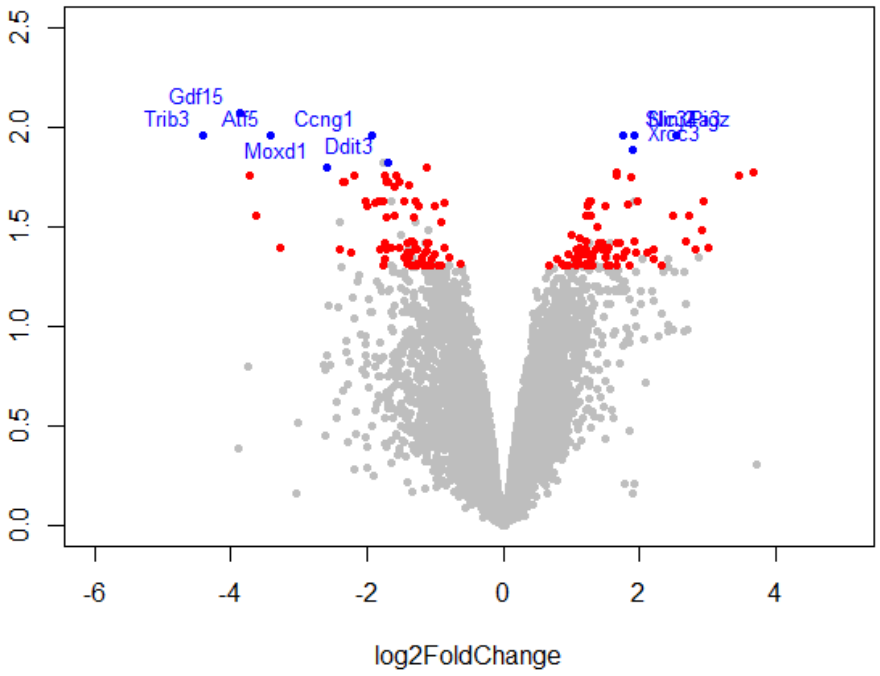


Figure 4.2. Volcano plot of –log10 of adjusted p-values and log fold change in the *corpus callosum* analysis. Significant differentially expressed genes (DEGs) are shown in red. The 10 most DEGs are shown in blue with the corresponding gene symbol.

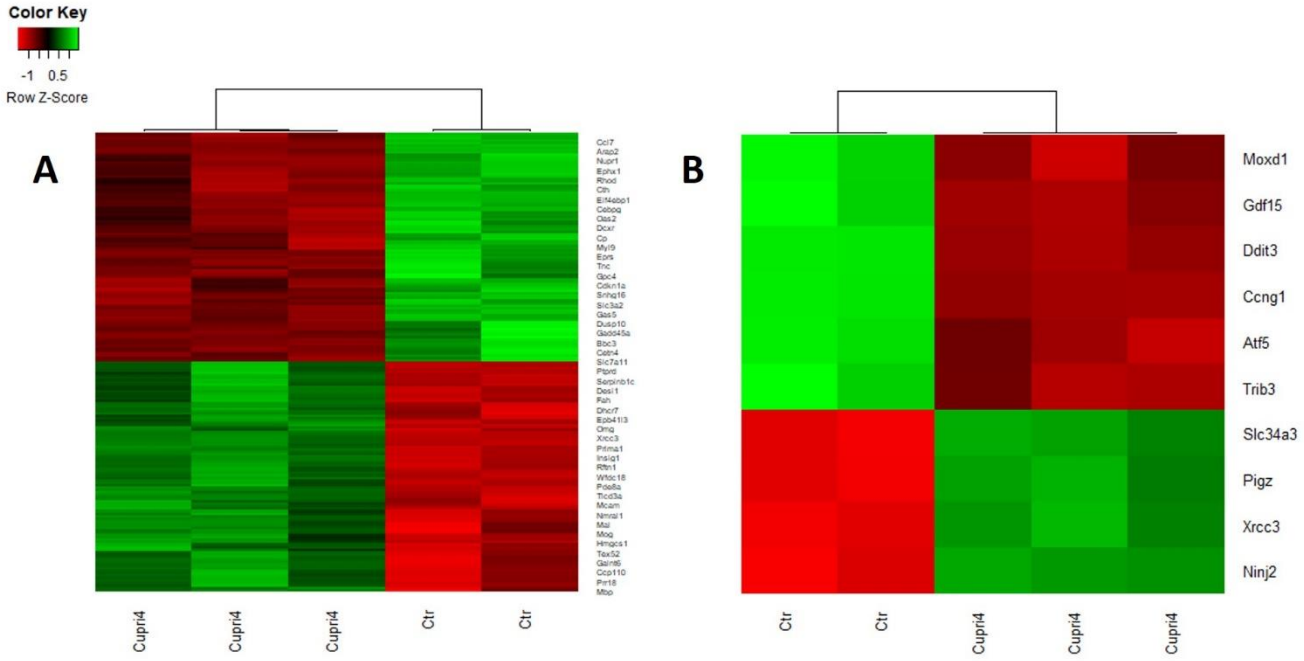


Figure 4.3. Heatmaps and hierarchical clustering performed with the normalized and filtered expression data and the samples included in the *corpus callosum* analysis, using all DEGs (A) or the 10 most DEGs (B). Green and red represent low and high gene expression, respectively.

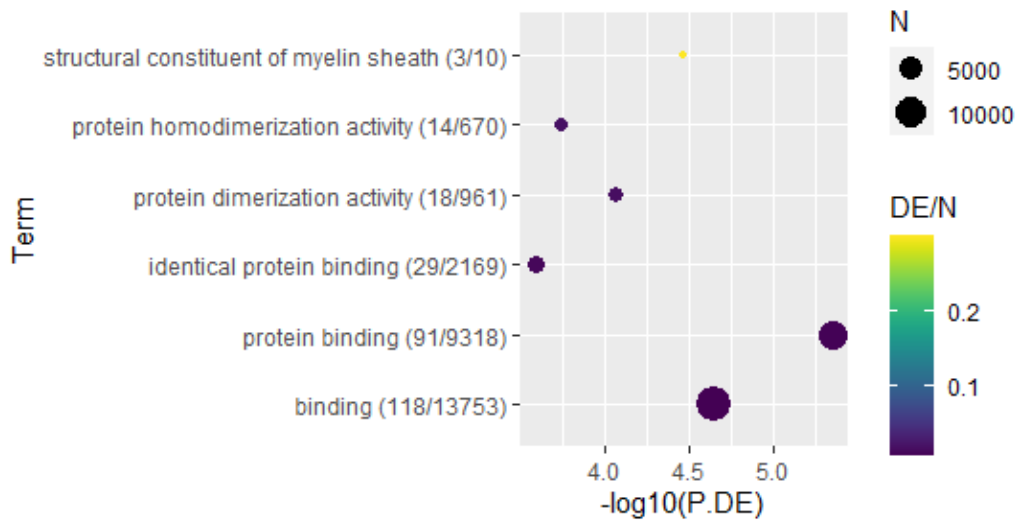


Figure 4.4. Dot plot of the most significant GO molecular functions associated with the DEGs identified in the *corpus callosum* analysis. The x-axis represents the -log10 of the p-value for over-representation of the GO term in the set. The color scale represents the number of DEGs in the differential expression set divided by the number of genes in the GO term. The dot size represents the number of genes in the GO term.

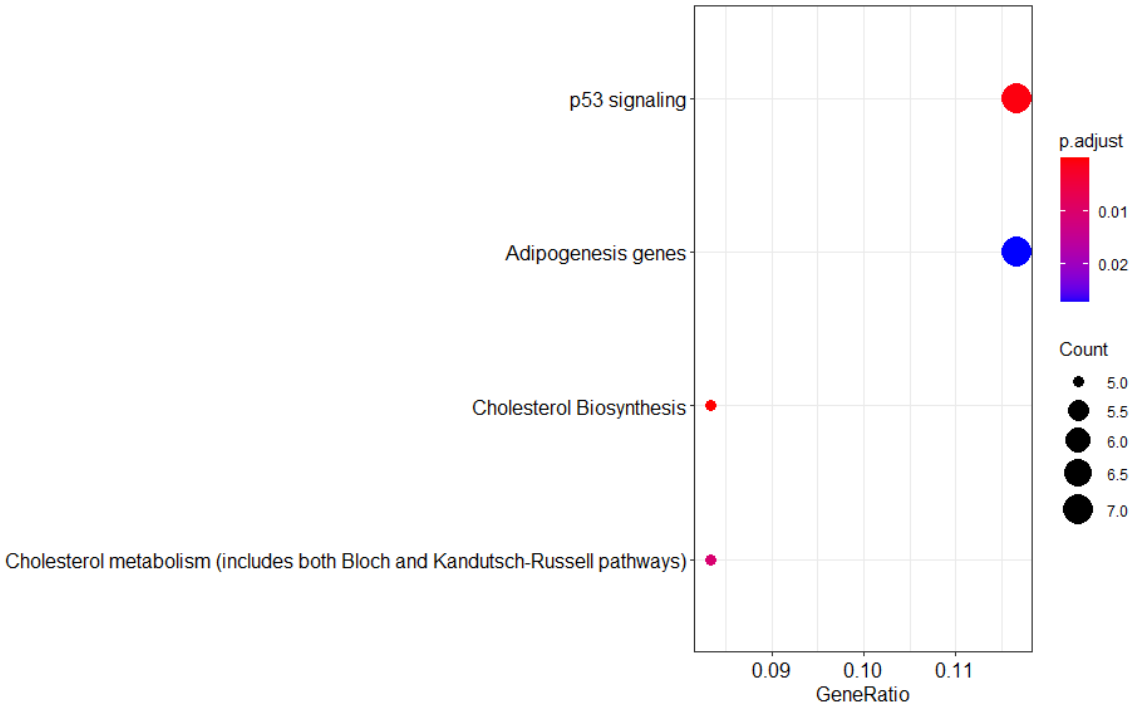


Figure 4.5. Dot plot of the significant WikiPathways associated with the DEGs identified in the corpus *callosum analysis*. The x-axis represents the number of DEGs in the differential expression set divided by the number of genes in the pathway. The color scale represents the adjusted p-value. The dot size represents the number of genes in the pathway.

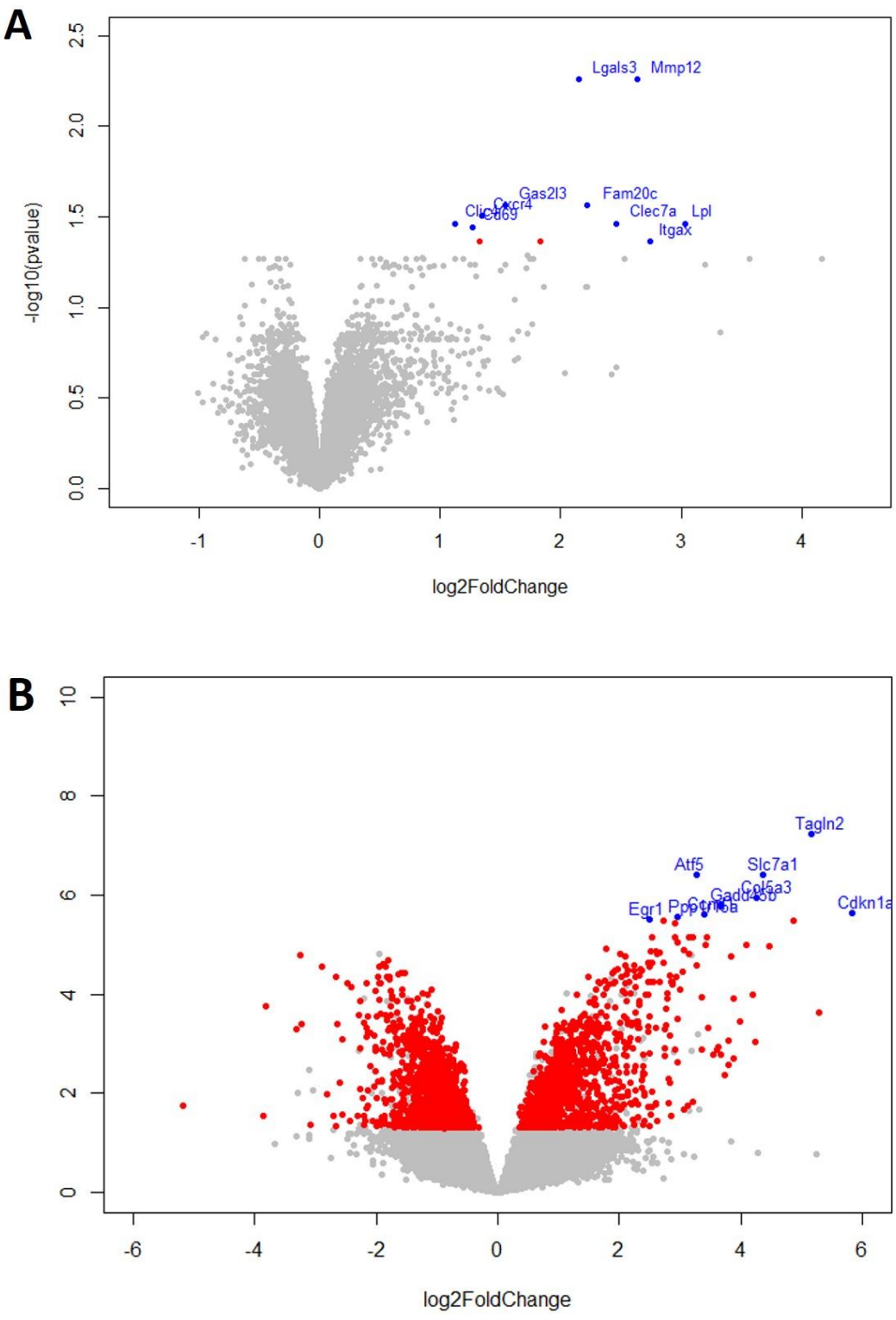


Figure 4.6. Volcano plots of –log10 of adjusted p-values and log fold changes in the microglia (A) and OPC (B) analyses. Significant DEGs are shown in red. The 10 most DEGs are shown in blue with the corresponding gene symbol.

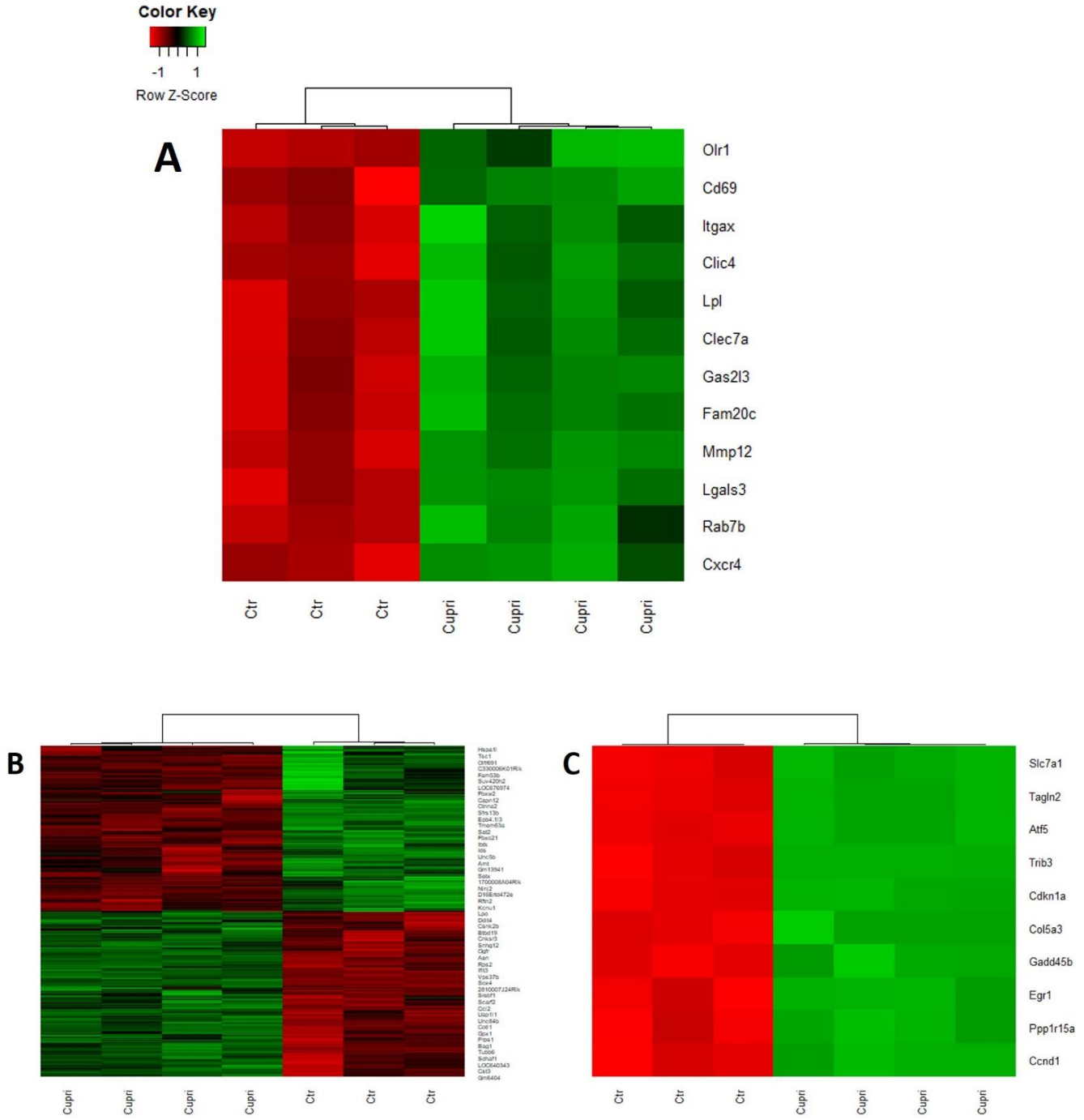


Figure 4.7. Heatmaps and hierarchical clustering performed with the normalized and filtered expression data and the samples included in the microglia (A) and OPC analysis (B-C). Heatmap with all DEGs (B) or with the 10 most DEGs from the OPC analysis (C). Green and red represent low and high gene expression, respectively.

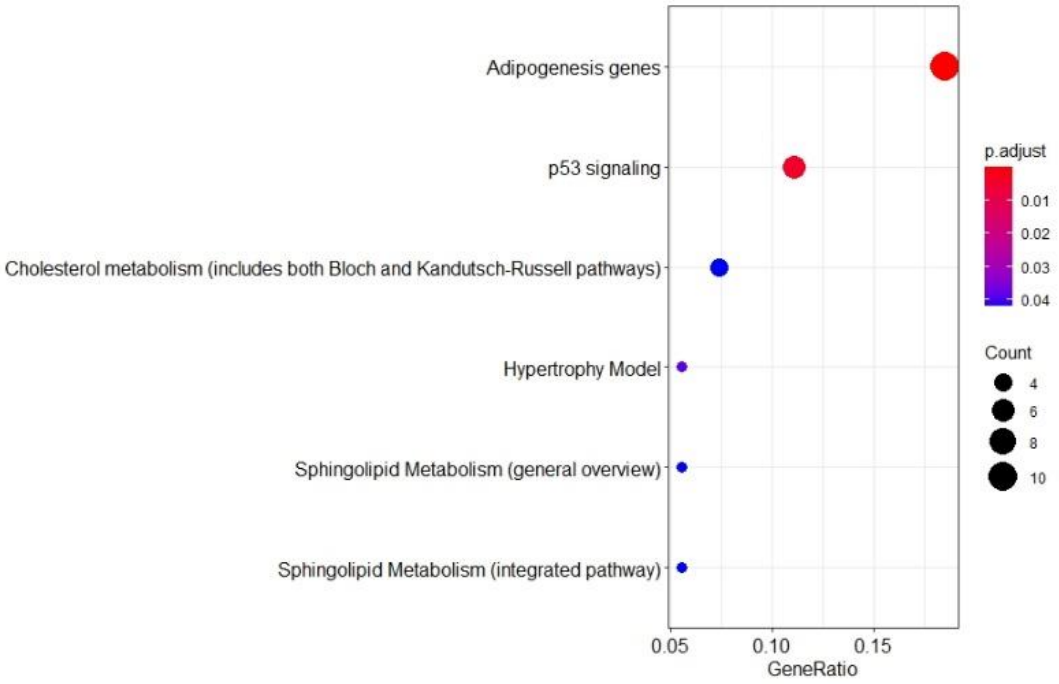


Figure 4.8. Dot plot of the significant WikiPathways associated with the DEGs identified in the OPC analysis. The x-axis represents the number of DEGs in the differential expression set divided by the number of genes in the pathway. The color scale represents the adjusted p-value. The dot size represents the number of genes in the pathway.

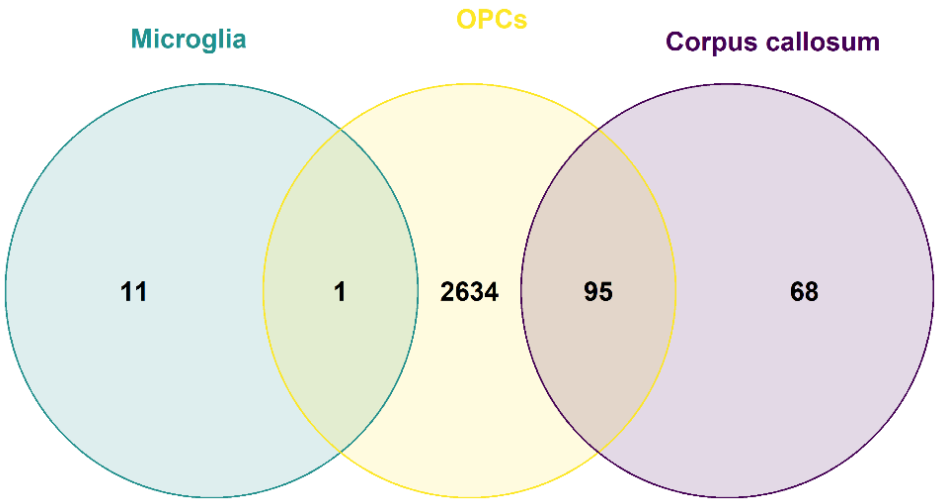


Figure 4.9. Venn diagram showing the number of common DEGs between the *corpus callosum*, microglia, and OPC analyses.

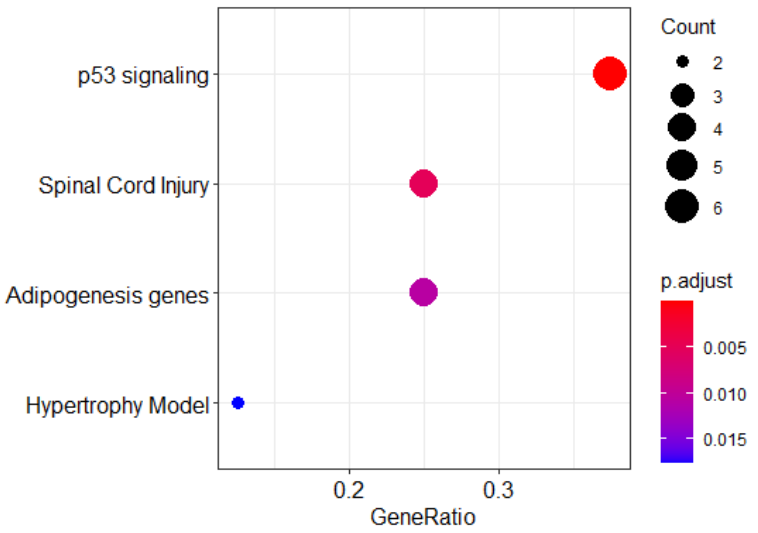


Figure 4.10. Wikipathways associated with the 95 DEGs identified in the *corpus callosum* and in the OPC analyses.

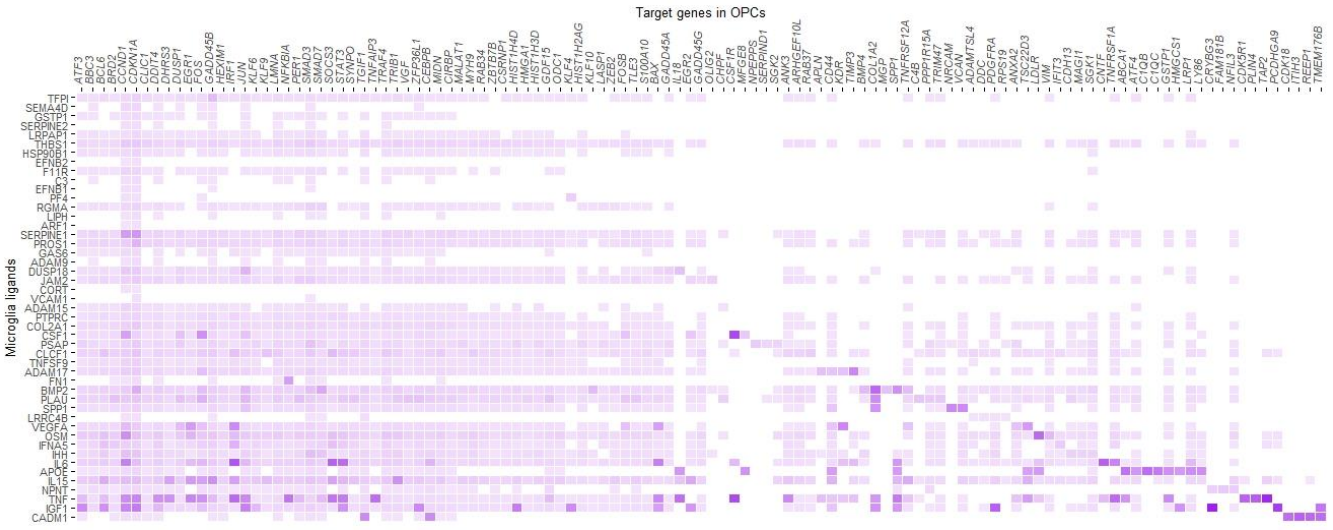


Figure 4.11. Identified microglia ligands and OPC target genes. Microglia expressed genes, OPC DEGs and NicheNet ligand-target matrix with regulatory potential scores were used. The darker the purple color the higher the regulatory potential of the microglia ligands on the OPC target genes.

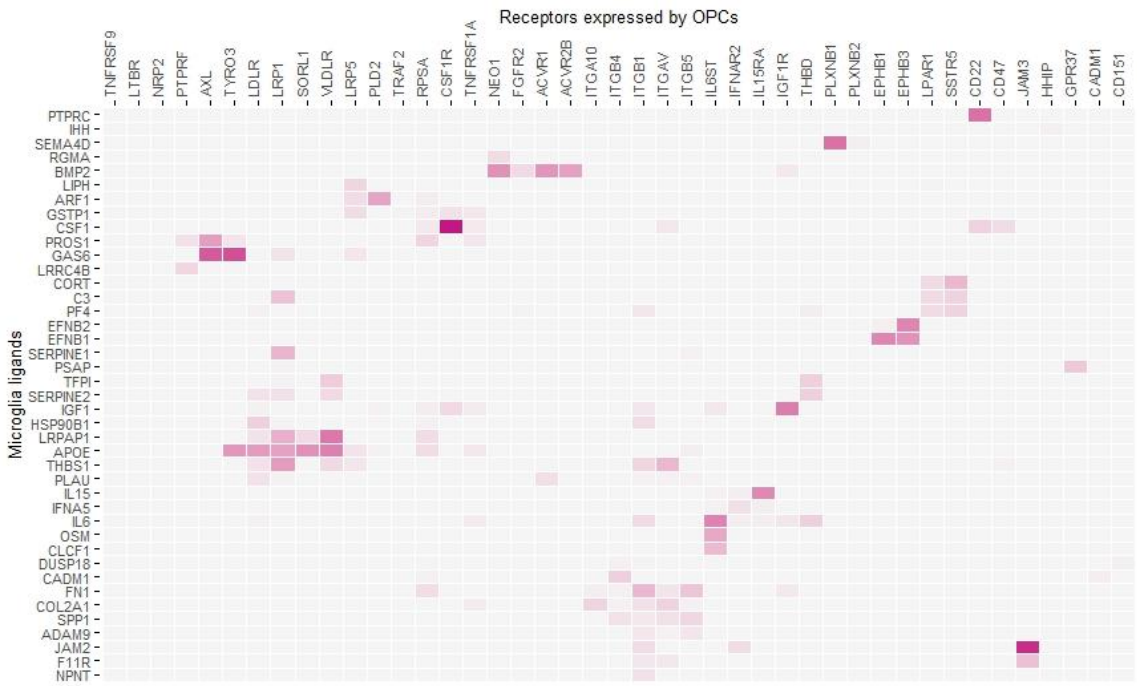


Figure 4.12. Identified microglia ligands and OPC receptors. Microglia expressed genes, OPC expressed genes, and NicheNet weights of the ligand-receptor interactions were used. The darker the pink color the larger the interaction potential between microglia ligands and OPC receptors.

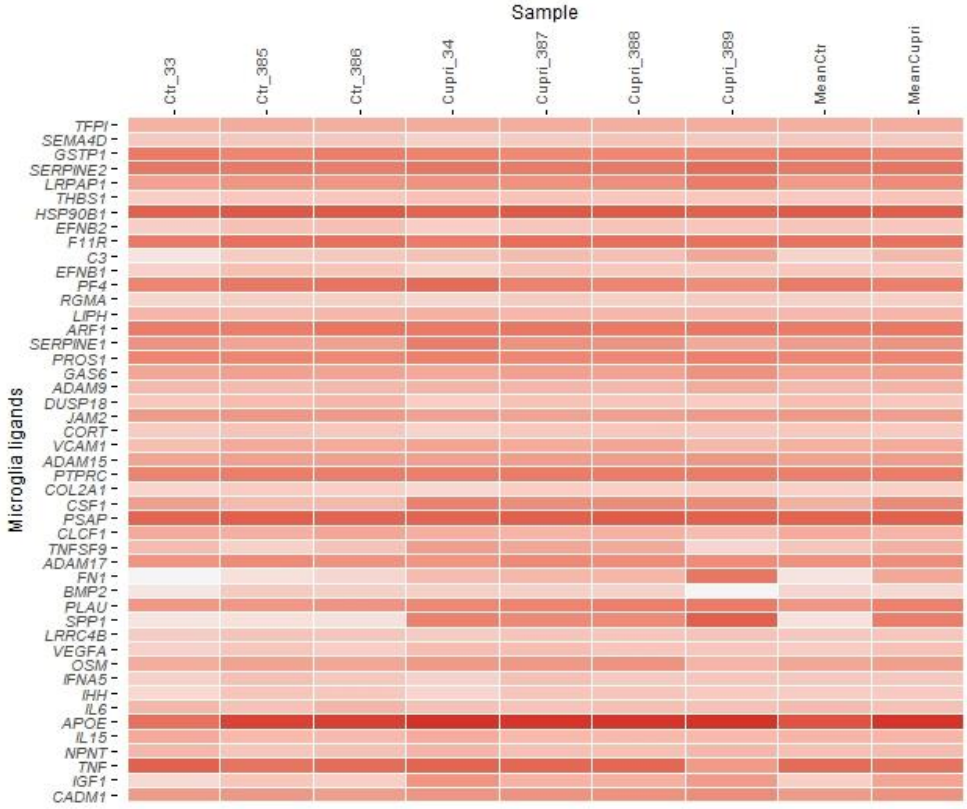


Figure 4.13. Expression of microglia ligands in the microglia samples from cuprizone treated (Cupri) and control mice (Ctr). The darker the red color the larger the expression of the microglia ligands.

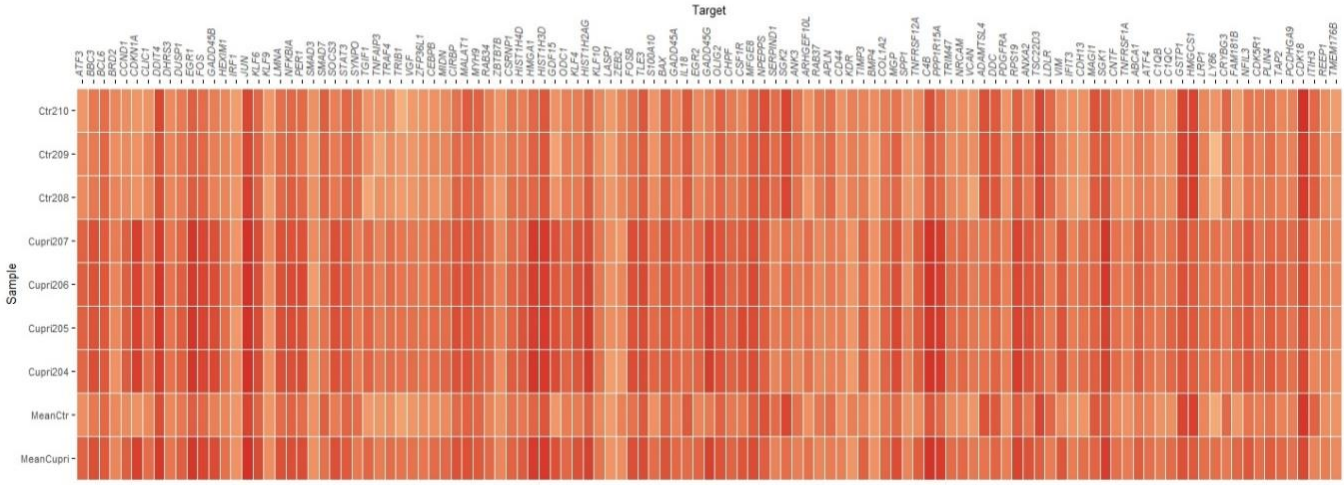


Figure 4.14. Expression of OPC target genes from microglia ligands in OPC samples from cuprizone treated (Cupri) and control mice (Ctr). The darker the red color the larger the expression of the OPC target genes.

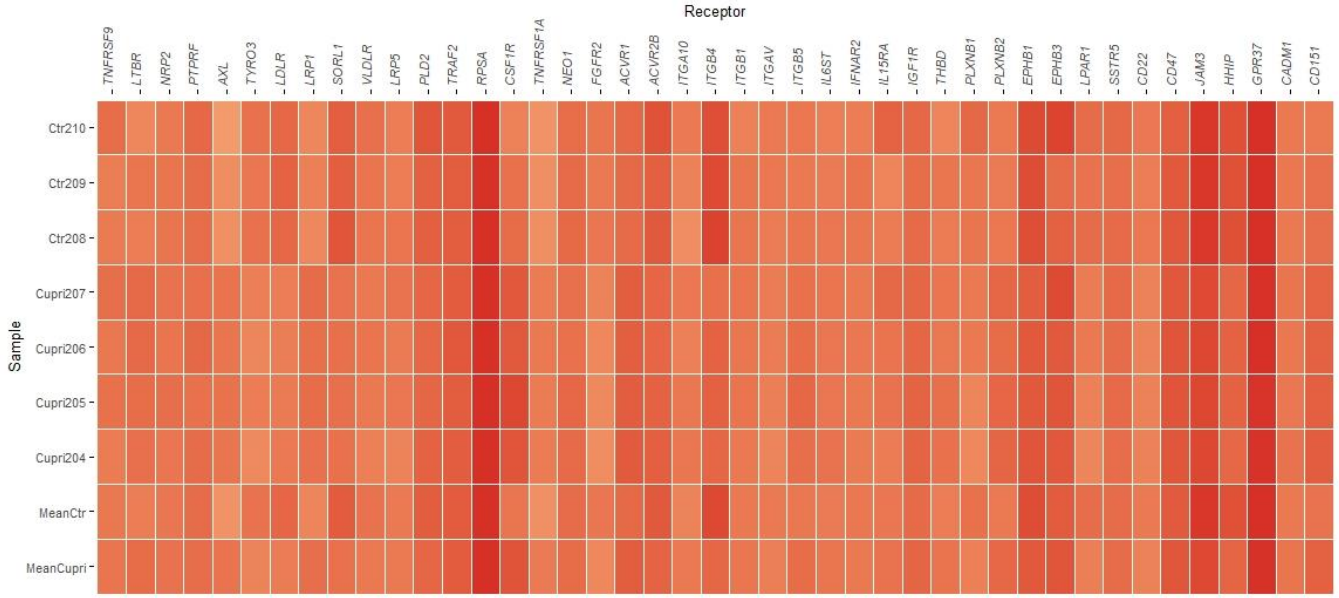


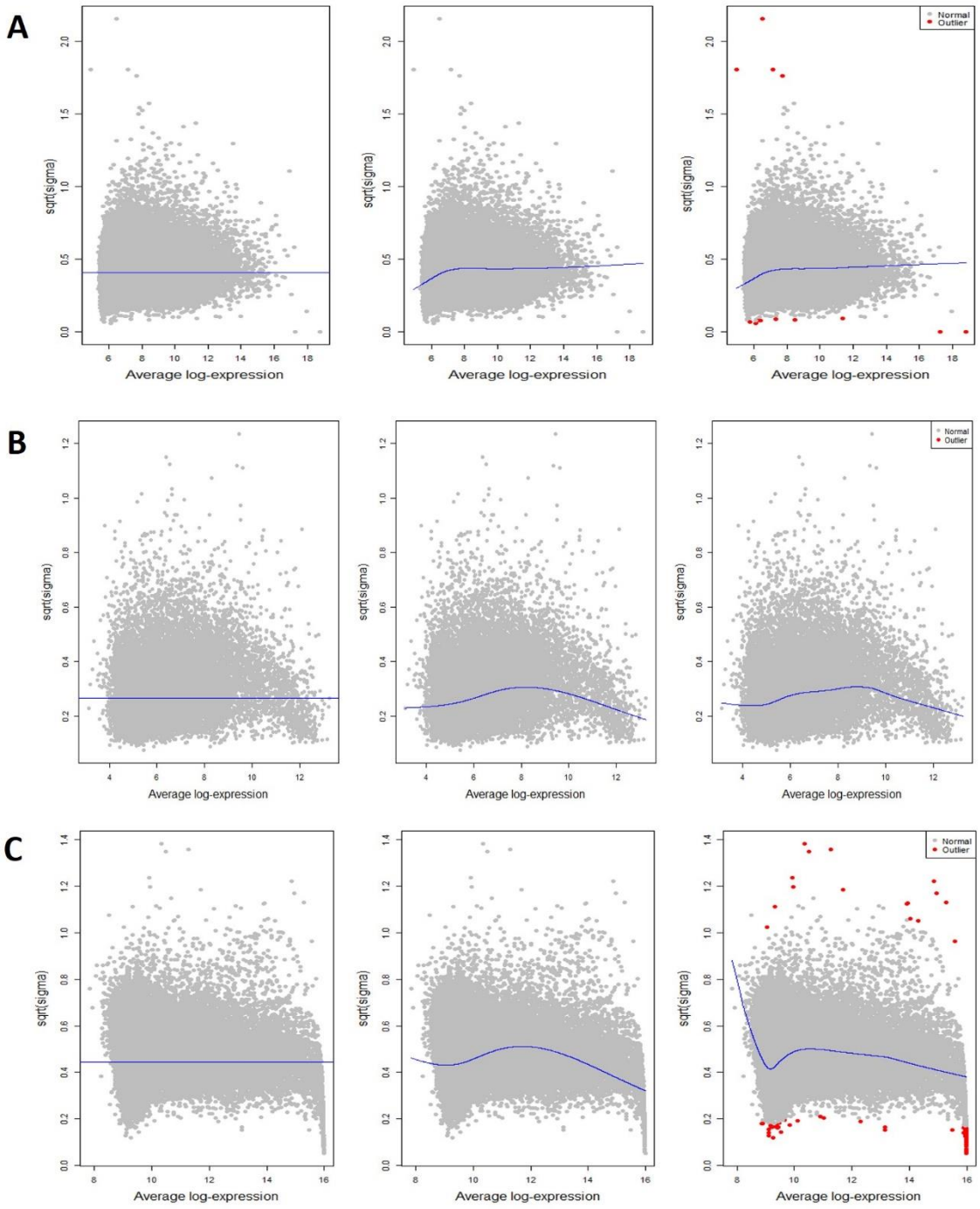
Figure 4.15. Expression of OPC receptors from microglia ligands in OPC samples from cuprizone treated (Cupri) and control mice (Ctr). The darker the red color the larger the expression of the OPC receptors.

7.3. Supplementary data

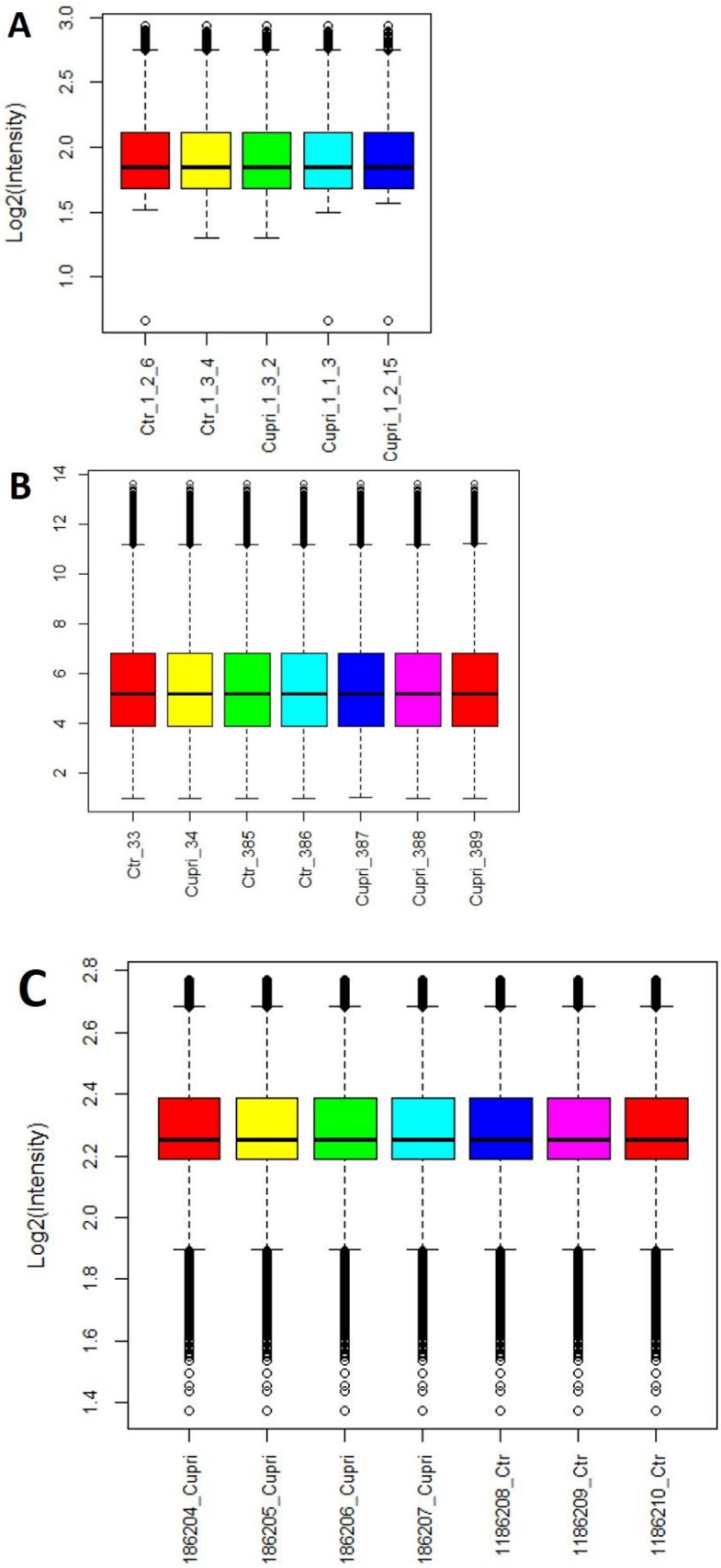
Supplementary Table 4.1. Number of probes before and after gene filtering, and number of DEGs after removal of duplicated/blanks.

	***Corpus callosum* first analysis with all samples**	***Corpus callosum* analysis with 5 samples**	**Microglia analysis**	**OPC analysis**
Probes before filtering	41267	41267	35556	39486
Probes with no symbol	7504	7504	11199	1
Control probes	92	92	--	--
Negative flagged probes	--	--	--	18
Low expression probes	9492	8493	6612	7421
Retained probes	24271	25270	17745	32046
Duplicated genes	--	26	--	622
Blank genes	--	--	--	1

DEGs	--	166	12	2730



Supplementary Figure 3.1. Plots of the residual standard deviation versus the average log expression for the fitted models in the *corpus callosum* (A), microglia (B), and OPC analysis (C). First graphs consider no trend in variance or outliers, second graphs consider a trend in variance and no outliers, while third graphs consider a trend in variance and outliers. Outliers are shown in red in the third graph.



Supplementary Figure 4.1. Boxplots of log-intensities after normalization in the samples used for the *corpus callosum* (A), microglia (B), and OPC analyses (C).

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