Supporting Information

CNS cell-type specific gene profiling of P301S tau transgenic mice identifies genes dysregulated by progressive tau accumulation

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Supporting Tables

Table S1 Differentially regulated genes in young and old TAU58/2 mice. Note that the differentially regulated genes from young and old TAU58/2 mice compared to the respective wild-type littermates are listed in individual tabs in the Excel table.

Table S2 MouseNetV2-predicted genes related to differentially regulated guide genes from young and old TAU58/2 mice. Note that the genes from young and old TAU58/2 mice are listed in individual tabs in the Excel table.

Supporting Figures

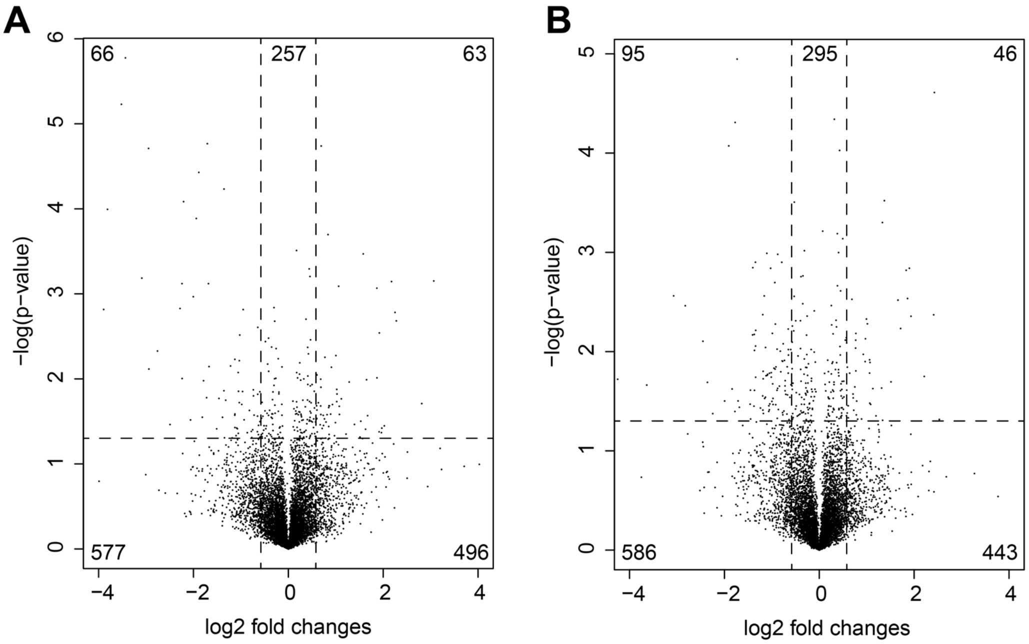

Figure S1 Cluster analysis and volcano blots of genes from young and old TAU58/2 mice.

(**A**) RNA sequencing of young TAU58/2 mice relative to non-transgenic littermate controls; Horizontal broken line indicates p-value of 0.05. Vertical broken lines indicated 50% down- (left) and up-regulation (right). Numbers of genes in gates areas are indicated. Note that for subsequent analysis all genes with differential expression >|50%| were included.

(**B**) RNA sequencing of old TAU58/2 mice relative to non-transgenic littermate controls; Horizontal broken line indicates p-value of 0.05. Vertical broken lines indicated 50% down- (left) and up-regulation (right). Numbers of genes in gates areas are indicated. Note that for subsequent analysis all genes with differential expression >|50%| were included.

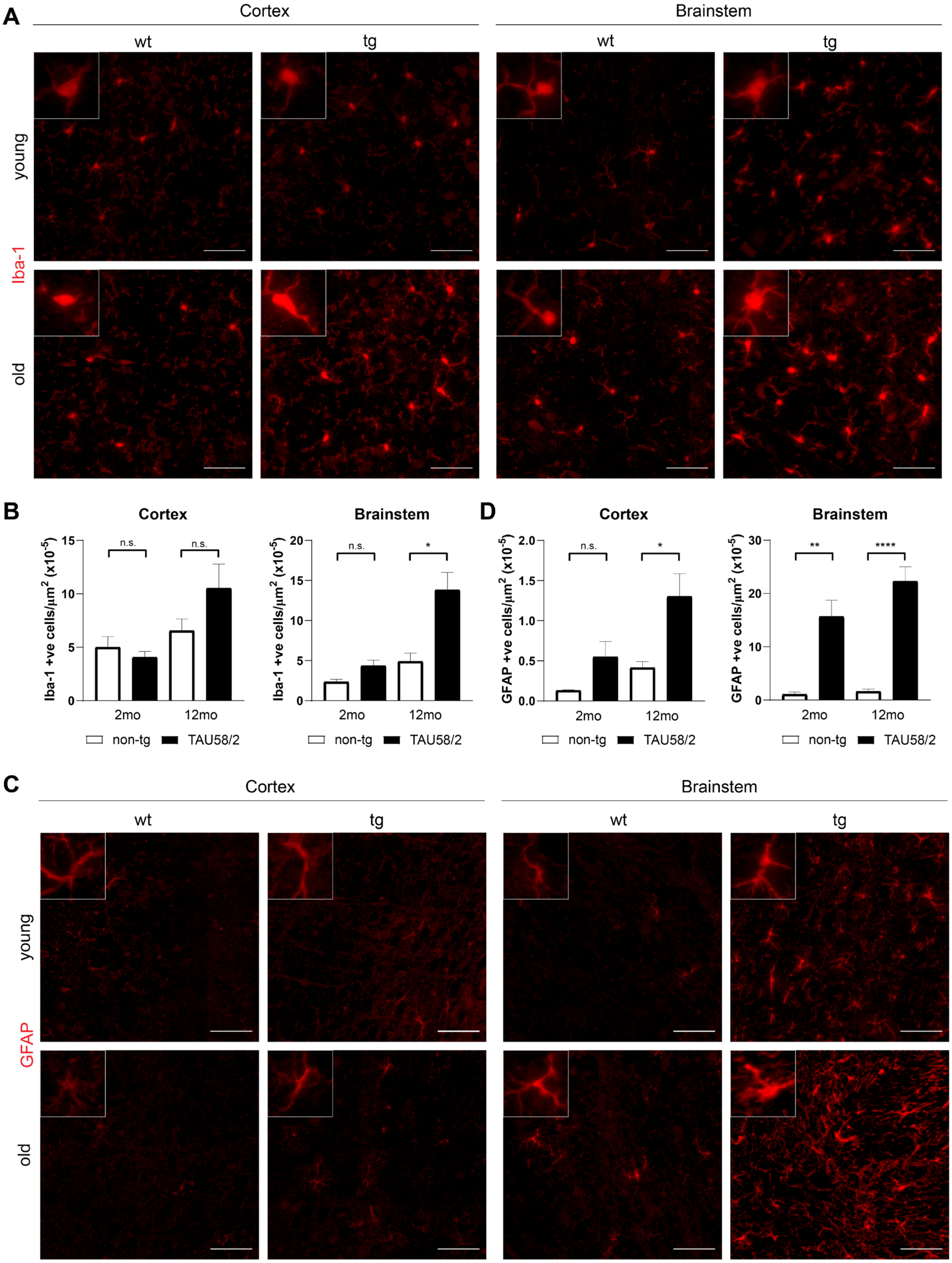
A
Cortex
Brainstem
wt
tg
wt
tg
young
Iba-1
old
B
Cortex
Iba-1 +ve cells/µm² (x10⁻⁵)
15
10
5
0
n.s.
n.s.
2mo
12mo
non-tg
TAU58/2
Brainstem
Iba-1 +ve cells/µm² (x10⁻⁵)
20
15
10
5
0
n.s.
*
2mo
12mo
non-tg
TAU58/2
D
Cortex
GFAP +ve cells/µm² (x10⁻⁵)
2.0
1.5
1.0
0.5
0.0
n.s.
*
2mo
12mo
non-tg
TAU58/2
Brainstem
GFAP +ve cells/µm² (x10⁻⁵)
30
20
10
0
**
****
2mo
12mo
non-tg
TAU58/2
C
Cortex
Brainstem
wt
tg
wt
tg
young
GFAP
old

Figure S2 Microgliosis and astrocytosis in TAU58/2 mice.

(**A**) Staining of young and old TAU58/2 and non-transgenic (non-tg) control brains with antibodies to microglial Iba1 (red). Representative images of cortex and brainstem are shown. Insets show higher resolution images of microglia. Scale bar, 50µm.

(**B**) Quantification of numbers of Iba1-positive microglia in cortex and brainstem of young and old TAU58/2 and non-transgenic (non-tg) control brains (tg: n=4-5, wt: n=3-4; *, $p<0.05$; Student's *t*-test).

(**C**) Staining of young and old TAU58/2 and non-transgenic (non-tg) control brains with antibodies to astrocytic Gfap (red). Representative images of cortex and brainstem are shown. Insets show higher resolution images of astrocytes. Scale bar, 50µm.

(**D**) Quantification of numbers of Gfap-positive astrocytes in cortex and brainstem of young and old TAU58/2 and non-transgenic (non-tg) control brains (tg: n=4-5, wt: n=3-4; **, $p<0.01$, ****, $p<0.0001$; Student's *t*-test).

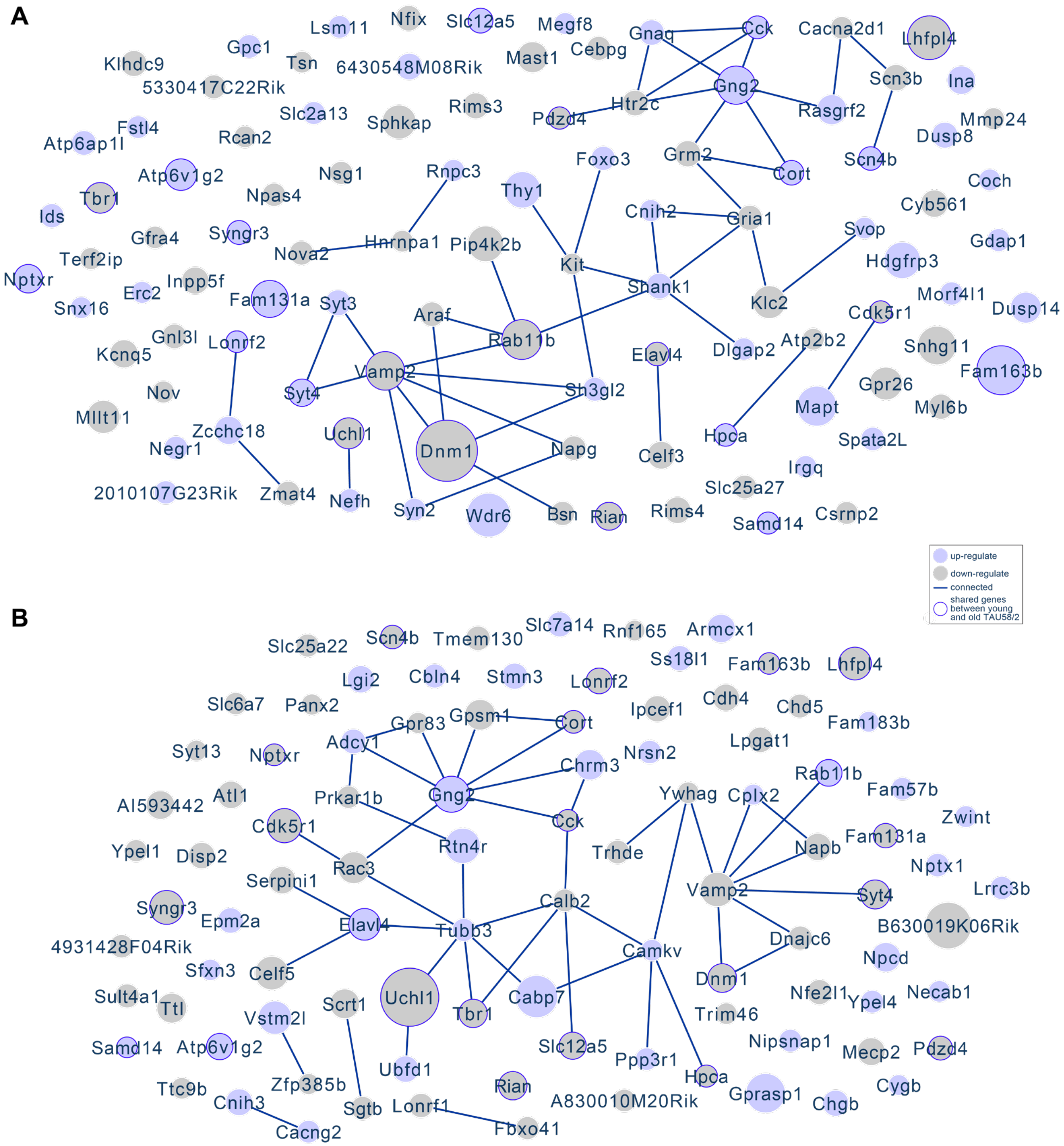

Figure S3 STRING analysis of differentially regulated genes annotated to neurons in young and old TAU58/2 mice.

(**A**) Complete predicted networks of differentially expressed genes annotated to neurons in young TAU58/2 mice. Light blue filled circles indicate up-regulated genes, while light grey filled circles indicate down-regulated genes. Size of filled circles indicate the relative degree of deregulation (large=highly deregulated and small=moderate deregulation as compared to gene expression in non-transgenic controls). Dark blue borders indicate deregulation in both young and old TAU58/2 mice. Lines indicate the connection predicted by STRING analysis.

(**B**) Complete predicted networks of differentially expressed genes annotated to neurons in old TAU58/2 mice.

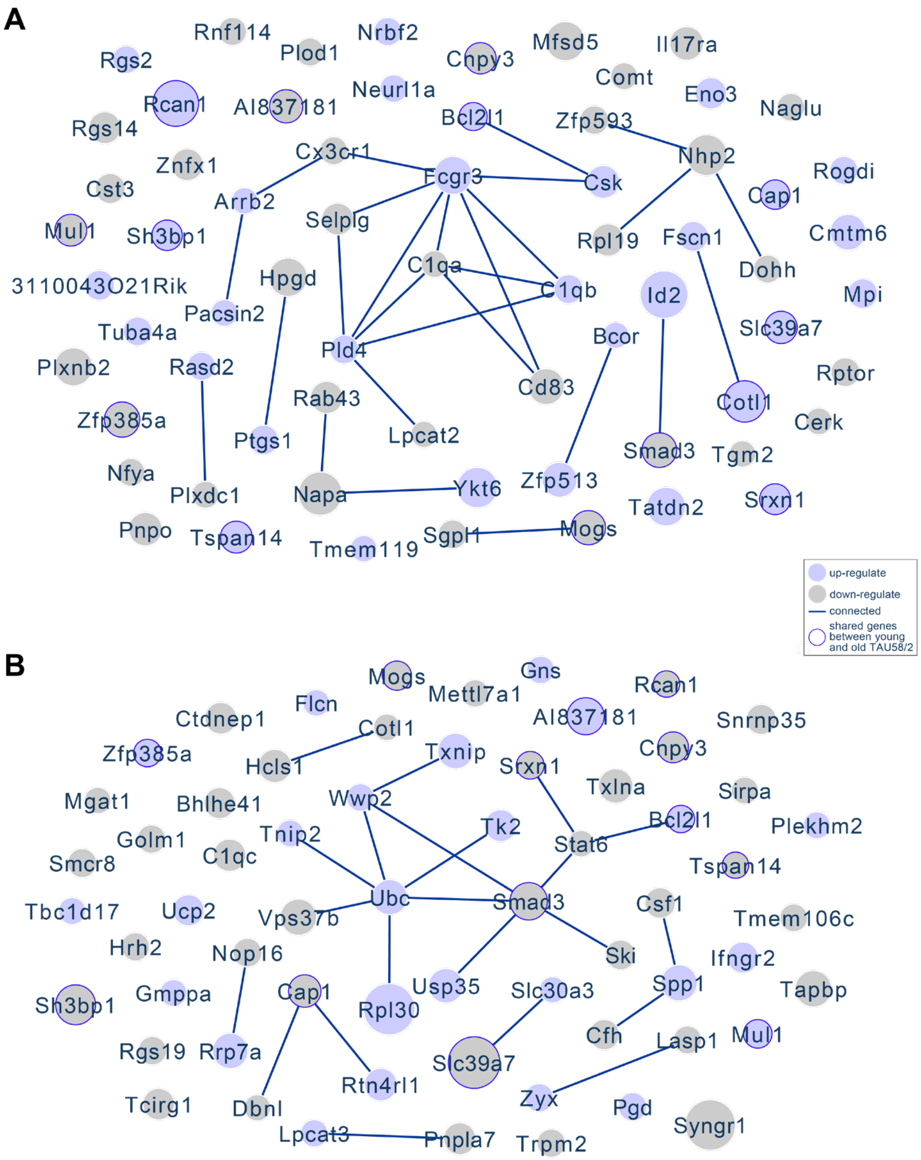

Figure S4 STRING analysis of differentially regulated genes annotated to microglia in young and old TAU58/2 mice.

(**A**) Complete predicted networks of differentially expressed genes annotated to microglia in young TAU58/2 mice. Light blue filled circles indicate up-regulated genes, while light grey filled circles indicate down-regulated genes. Size of filled circles indicate the relative degree of deregulation (large=highly deregulated and small=moderate deregulation as compared to gene expression in non-transgenic controls). Dark blue borders indicate deregulation in both young and old TAU58/2 mice. Lines indicate the connection predicted by STRING analysis.

(**B**) Complete predicted networks of differentially expressed genes annotated to microglia in old TAU58/2 mice.

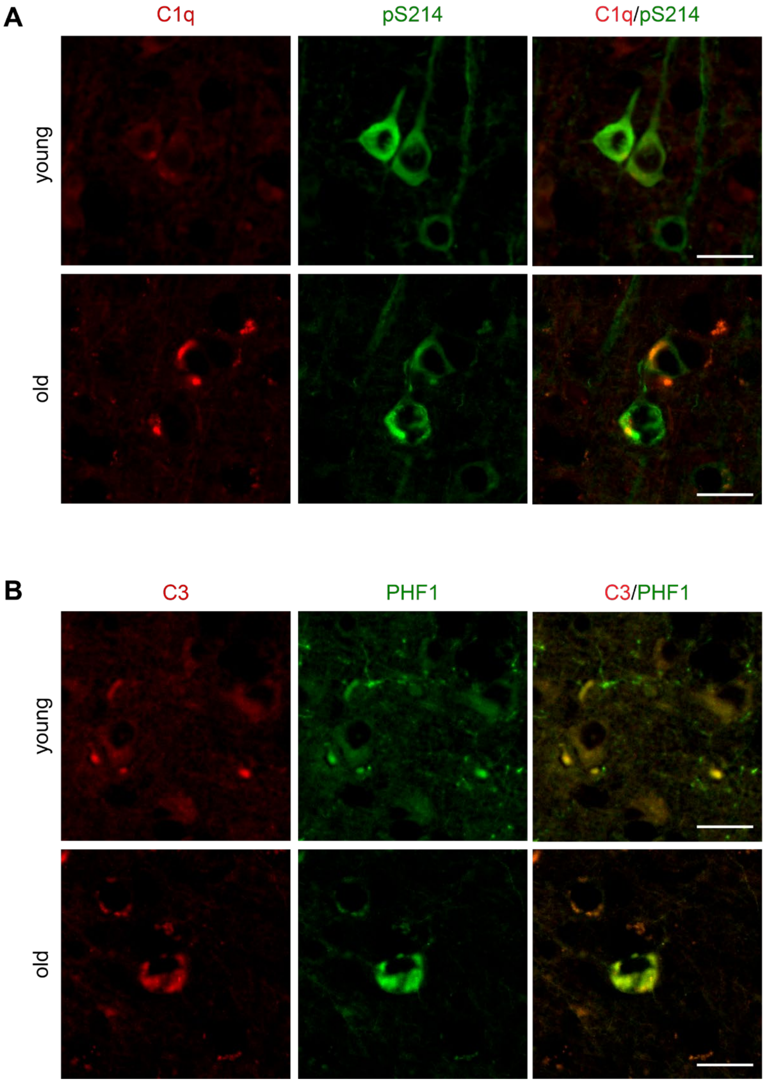

Figure S5 Complement activation and accumulation in phosphorylated tau-harboring neurons in brains of TAU58/2 mice.

(**A**) Staining of young and old TAU58/2 brains with antibodies to complement factor C1q (red) and phosphorylated tau (pS214). Scale bar, 50µm.

(**B**) Staining of young and old TAU58/2 brains with antibodies to complement factor C3 (red) and phosphorylated tau (PHF1). Scale bar, 50µm.

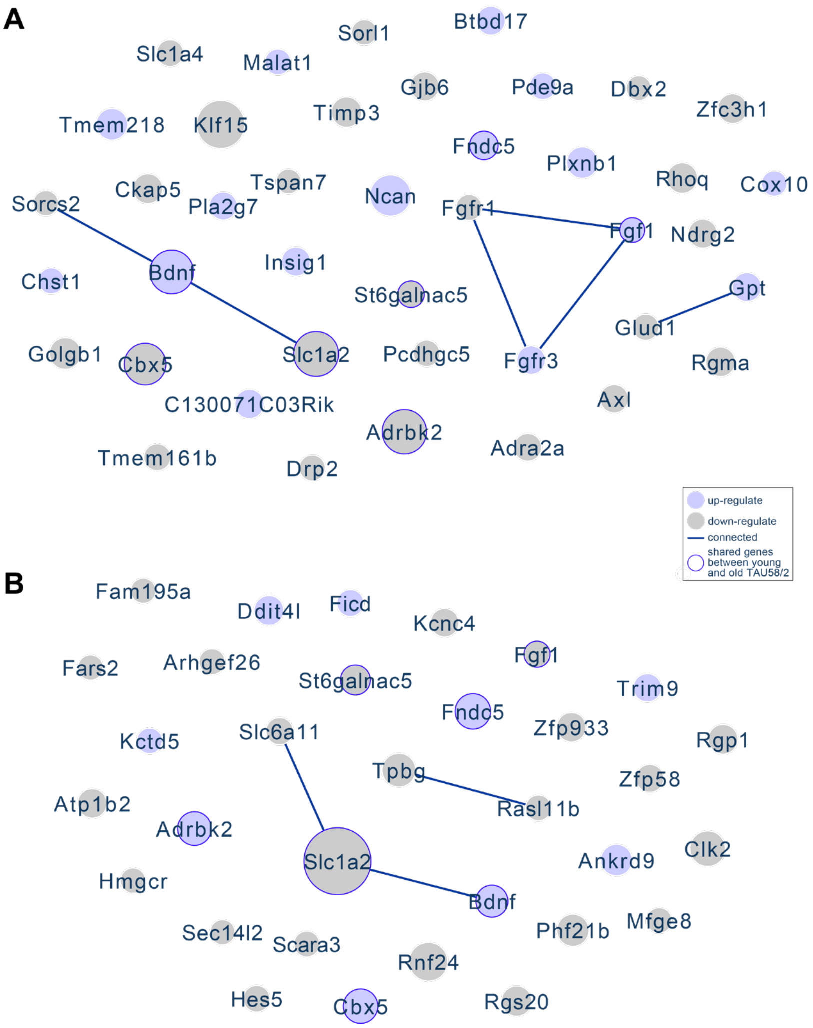

Figure S6 STRING analysis of differentially regulated genes annotated to astrocytes in young and old TAU58/2 mice.

(**A**) Complete predicted networks of differentially expressed genes annotated to astrocytes in young TAU58/2 mice. Light blue filled circles indicate up-regulated genes, while light grey filled circles indicate down-regulated genes. Size of filled circles indicate the relative degree of deregulation (large=highly deregulated and small=moderate deregulation as compared to gene expression in non-transgenic controls). Dark blue borders indicate deregulation in both young and old TAU58/2 mice. Lines indicate the connection predicted by STRING analysis.

(**B**) Complete predicted networks of differentially expressed genes annotated to astrocytes in old TAU58/2 mice.

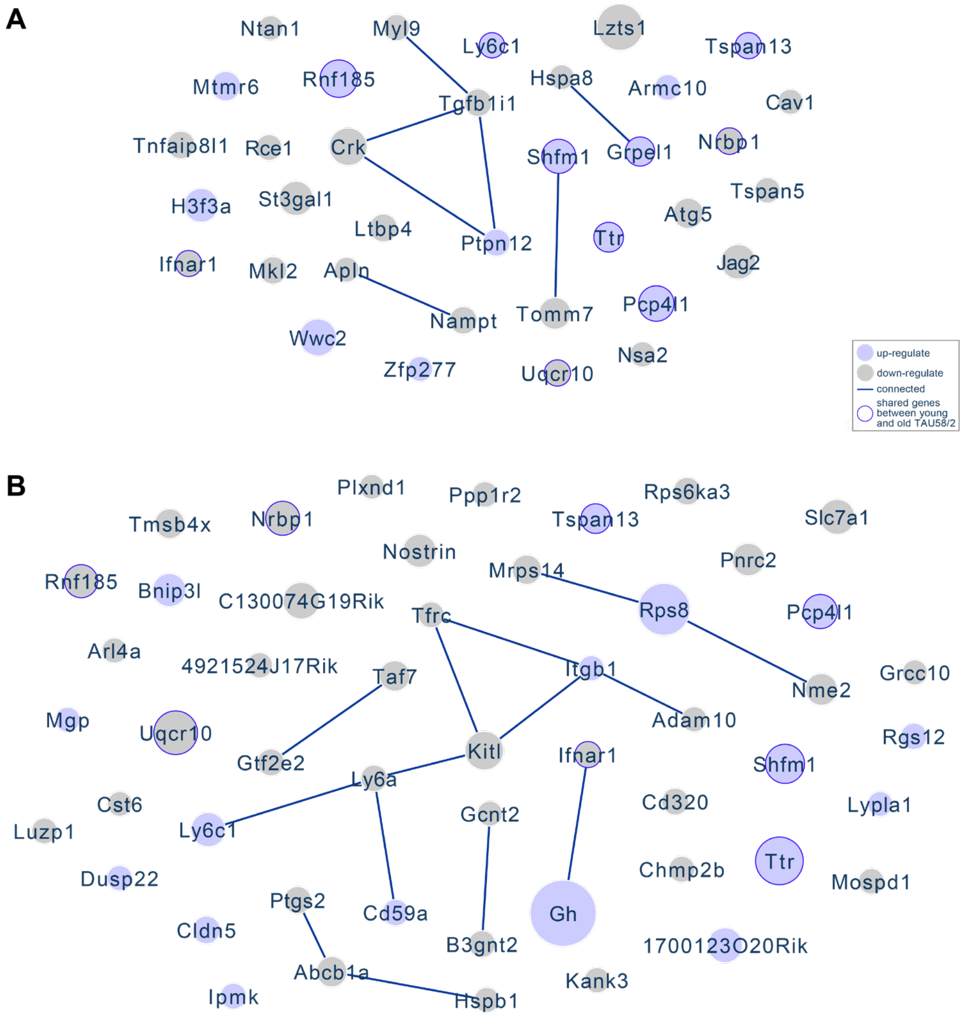

Figure S7 STRING analysis of differentially regulated genes annotated to endothelial cells in young and old TAU58/2 mice.

(**A**) Complete predicted networks of differentially expressed genes annotated to endothelial cells in young TAU58/2 mice. Light blue filled circles indicate up-regulated genes, while light grey filled circles indicate down-regulated genes. Size of filled circles indicate the relative degree of deregulation (large=highly deregulated and small=moderate deregulation as compared to gene expression in non-transgenic controls). Dark blue borders indicate deregulation in both young and old TAU58/2 mice. Lines indicate the connection predicted by STRING analysis.

(**B**) Complete predicted networks of differentially expressed genes annotated to endothelial cells in old TAU58/2 mice.

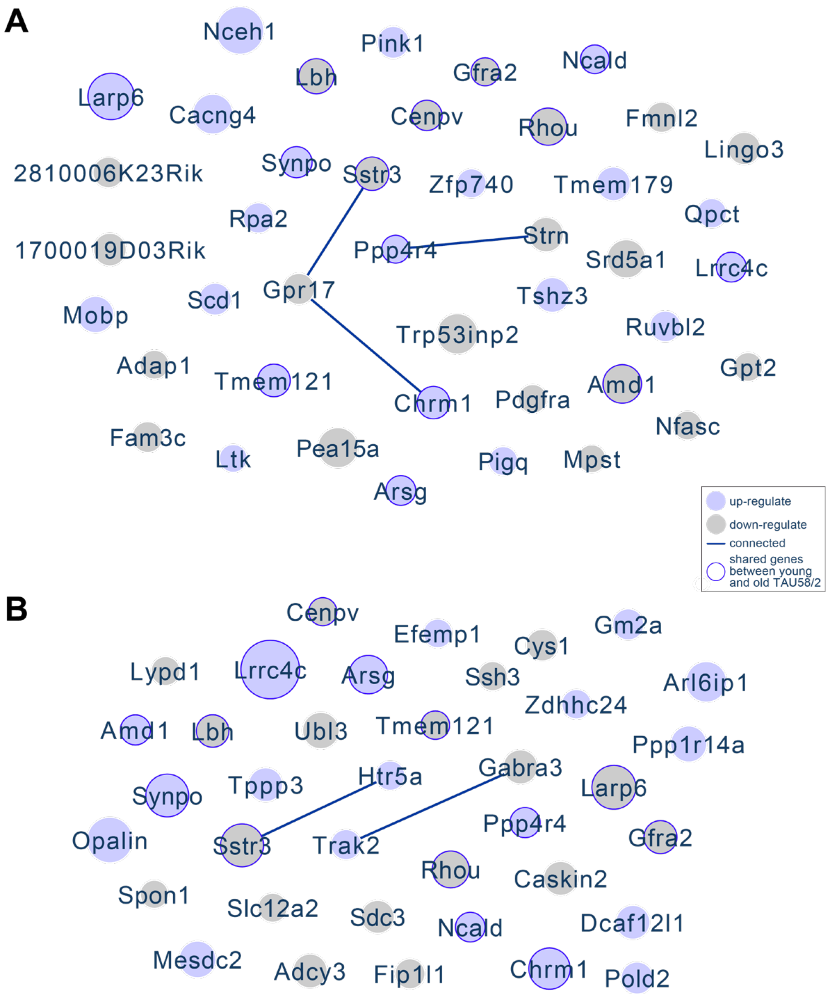

Figure S8 STRING analysis of differentially regulated genes annotated to oligodendrocytes in young and old TAU58/2 mice.

(**A**) Complete predicted networks of differentially expressed genes annotated to oligodendrocytes in young TAU58/2 mice. Light blue filled circles indicate up-regulated genes, while light grey filled circles indicate down-regulated genes. Size of filled circles indicate relative degree of deregulation (large=highly deregulated and small=moderate deregulation as compared to gene expression in non-transgenic controls). Dark blue borders indicate deregulation in both young and old TAU58/2 mice. Lines indicate the connection predicted by STRING analysis.

(**B**) Complete predicted networks of differentially expressed genes annotated to oligodendrocytes in old TAU58/2 mice.