

SUPPLEMENTAL METHODS

Genomic Control

The empirical null distribution in GWAS has been shown to be altered by global variance inflation due to underlying population stratification and cryptic relatedness¹ and deflation due to over-correction of test statistics for polygenic traits by standard genomic control techniques². We utilized a control method that leverages only intergenic SNPs, which are likely depleted for true associations³. First, we annotated the SNPs to genic (5'UTR, exon, intron, 3'UTR) and intergenic regions using information from the 1,000 genomes project (1KGP). For each phenotype, we estimated the genomic inflation factor λ_{GC} given the effect sizes of associations with intergenic SNPs. The inflation factor, λ_{GC} is the median of non-central parameters of chi-square statistics divided by the expected median of a chi-square distribution with one degree of freedom. Once inflation factor is derived, we then divided all test statistics by λ_{GC} .

Conjunction statistics – test of association with both phenotypes

We defined the conjunction statistics (denoted as FDR Trait1 & Trait2) as the maximum of the conditional FDR in both directions, i.e. $\text{FDR Trait1 \& Trait2} = \max(\text{FDR Trait1} \mid \text{Trait2}, \text{FDR Trait2} \mid \text{Trait1})$ based on the combination of p-value for the SNP in PSP and PD, FTD, or AD^{4,5}. The FDR given trait pairs is estimated through interpolating the observed conditional effects into 2D look-up table. The conjunction statistic allows for identification of SNPs that are associated with both phenotypes, which minimizes the effect of a single phenotype driving the common association signal. Table 2 lists all SNPs with

conjunction $FDR < 0.05$ ($-\log_{10}(FDR) > 1.3$) with PSP and PD, FTD, and AD after removing all SNPs with $r^2 > 0.2$ based on 1KGP linkage disequilibrium (LD) (pruning).

Conjunction FDR Manhattan plots

To illustrate the localization of the genetic markers associated with PSP given PD, FTD, or AD we used a 'Conjunction FDR Manhattan plot', plotting all SNPs within an LD block in relation to their chromosomal location. As illustrated in Figure 1b within the main manuscript, the large points represent the SNPs with $FDR < 0.05$, whereas the small points represent the non-significant SNPs. All SNPs before 'pruning' (removing all SNPs with $r^2 > 0.2$ based on 1KGP LD structure) are shown. The strongest signal in each LD block is illustrated with a black line around the circles. This was identified by ranking all SNPs in increasing order, based on the conditional FDR value for PSP, and then removing SNPs in LD $r^2 > 0.2$ with any higher ranked SNP. Thus, the selected locus was the most significantly associated with PSP in each LD block for PD, FTD, or AD.

IGAP Cohort

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2. In this study, we focused on the stage 1 IGAP SNPs.

SUPPLEMENTAL RESULTS

Relationship between CXCR4, TMEM119 and AIF1 in transgenic mouse model

Within the hippocampus, across all evaluated time points (2,4,6 and 18 months) for wild-type and Tau-P301L mice, we found a relationship between *CXCR4* and *TMEM119* (Pearson's $R = 0.52$, $p = 5.3 \times 10^{-5}$) and *AIF1* (Pearson's $R = 0.52$, $p = 5.2 \times 10^{-5}$). Within the cortex, we found no relationship between *CXCR4* and *TMEM119* (Pearson's $R = 0.17$, $p = 0.21$) and *AIF1* (Pearson's $R = 0.13$, $p = 0.32$). Within the cerebellum, we found no relationship between *CXCR4* and *TMEM119* (Pearson's $R = 0.20$, $p = 0.13$) and *AIF1* (0.05 , $p = 0.68$).

Relationship between CXCR4 associated genes, TMEM119 and AIF1 in transgenic mouse model

We also assessed the relationship between *CXCR4* associated genes (*CXCL12*, *RALB*, *CCR5* and *TLR2*) and *TMEM119* and *AIF1*. Within the hippocampus, across all evaluated time points (2,4,6 and 18 months) for wild-type and Tau-P301L mice, we found a relationship between *CCR5* and *TMEM119* (Pearson's $R = 0.58$, $p = 3.5 \times 10^{-6}$) and *AIF1* (Pearson's $R = 0.63$, $p = 2.4 \times 10^{-7}$). Similarly within the hippocampus, we also found a relationship between *TLR2* and *TMEM119* (Pearson's $R = 0.71$, $p = 1.3 \times 10^{-9}$) and *AIF1* (Pearson's $R = 0.86$, $p = 2.2 \times 10^{-16}$). In contrast we found no association between *TMEM119* and *AIF1* and *CXCL12* (Pearson's $R = -0.119$, $p = 0.38$ and Pearson's $R = -0.05$, $p = 0.69$, respectively), and *RALB* (Pearson's $R = 0.13$, $p = 0.35$ and Pearson's $R = 0.23$, $p = 0.09$, respectively) within the hippocampus.

Within the cortex, we found a significant association between *TMEM119* and *AIF1* and *TLR2* (Pearson's $R = 0.51$, $p = 6.8 \times 10^{-5}$ and Pearson's $R = 0.83$, $p = 1.34 \times 10^{-15}$, respectively), and *CCR5* (Pearson's $R = 0.58$, $p = 2.3 \times 10^{-6}$ and Pearson's $R = 0.55$, $p = 1.4 \times 10^{-5}$, respectively). In contrast we found no relationship between *TMEM119* and *AIF1* and either *RALB* or *CXCL12* (all p -values > 0.05) within the cortex.

Within the cerebellum, we found a significant association between *TMEM119* and *AIF1* and *TLR2* (Pearson's $R = 0.64$, $p = 1.1 \times 10^{-7}$ and Pearson's $R = 0.86$, $p = < 2.2 \times 10^{-16}$, respectively), and *CCR5* (Pearson's $R = 0.63$, $p = 2.3 \times 10^{-7}$ and Pearson's $R = 0.68$, $p = 9.4 \times 10^{-9}$, respectively). In contrast we found no relationship between *TMEM119* and *AIF1* and either *RALB* or *CXCL12* (all p -values > 0.05) within the cerebellum.

TMEM119 and AIF1 expression is elevated in tau transgenic mouse model

Within the hippocampus, *TMEM119* ($F = 42.9$, $p = 3.9 \times 10^{-8}$) and *AIF1* ($F = 149.6$, $p = < 2.0 \times 10^{-16}$) were elevated over time. Within the cortex, we found that *AIF1* ($F = 12.7$, $p = 0.008$) was elevated over time; in contrast, *TMEM119* expression was not altered over time ($F = 1.1$, $p = 0.29$). Within the cerebellum, we found that expression of *TMEM119* ($F = 2.7$, $p = 0.11$) and *AIF1* ($F = 2.1$, $p = 0.15$) was not altered over time.

SUPPLEMENTAL REFERENCES

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SUPPLEMENTAL FIGURES

Supplemental Figure 1. Linkage disequilibrium within PSP and PD risk loci. **(a)**

Plot for rs749873. **(b)** Plot for rs199533.

Supplemental Figure 2. Line plots illustrating *MAPT* gene expression in tau transgenic (red line) and wild-type mice (black line) from 2 to 18 months of age, across the (a) hippocampus, (b) cortex, and (c) cerebellum. Total tau pathology (d) over time is also illustrated.

Supplemental Figure 3. Line plots illustrating *TLR2* gene expression in tau transgenic (red line) and wild-type mice (black line) from 2 to 18 months of age, across the (a) hippocampus, (b) cortex, and (c) cerebellum. Total tau pathology (d) over time is also illustrated.

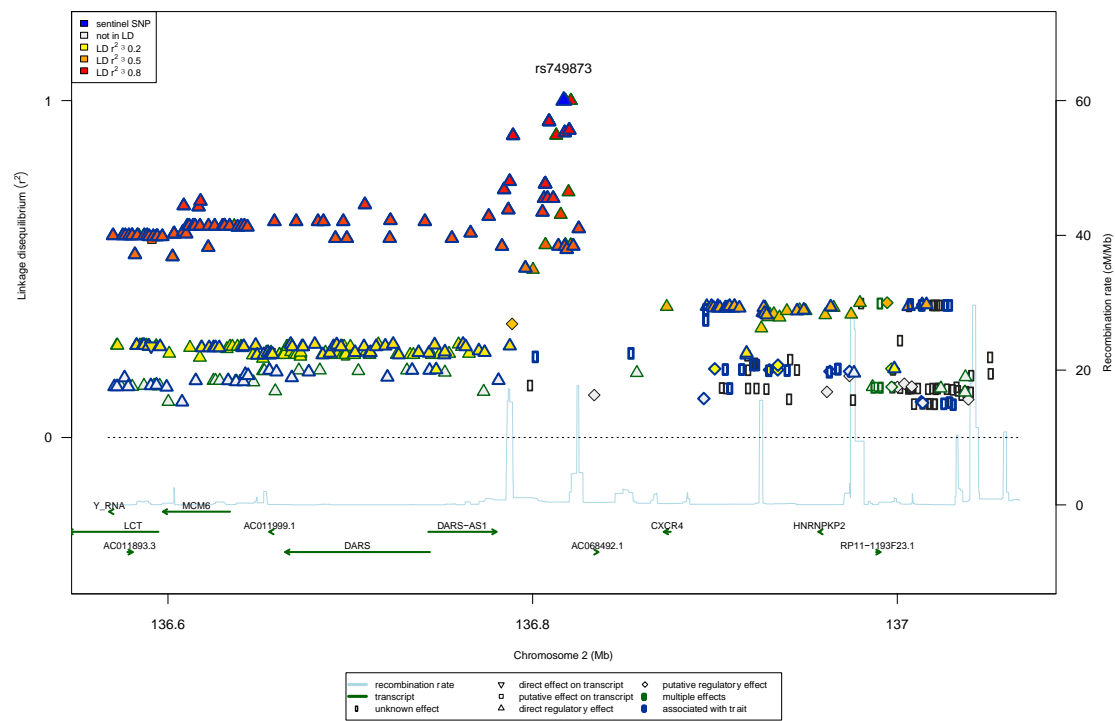
Supplemental Figure 4. Line plots illustrating *CCR5* gene expression in tau transgenic (red line) and wild-type mice (black line) from 2 to 18 months of age, across the (a) hippocampus, (b) cortex, and (c) cerebellum. Total tau pathology (d) over time is also illustrated.

Supplemental Figure 5. Line plots illustrating *CXCL12* gene expression in tau transgenic (red line) and wild-type mice (black line) from 2 to 18 months of age, across the (a) hippocampus, (b) cortex, and (c) cerebellum. Total tau pathology

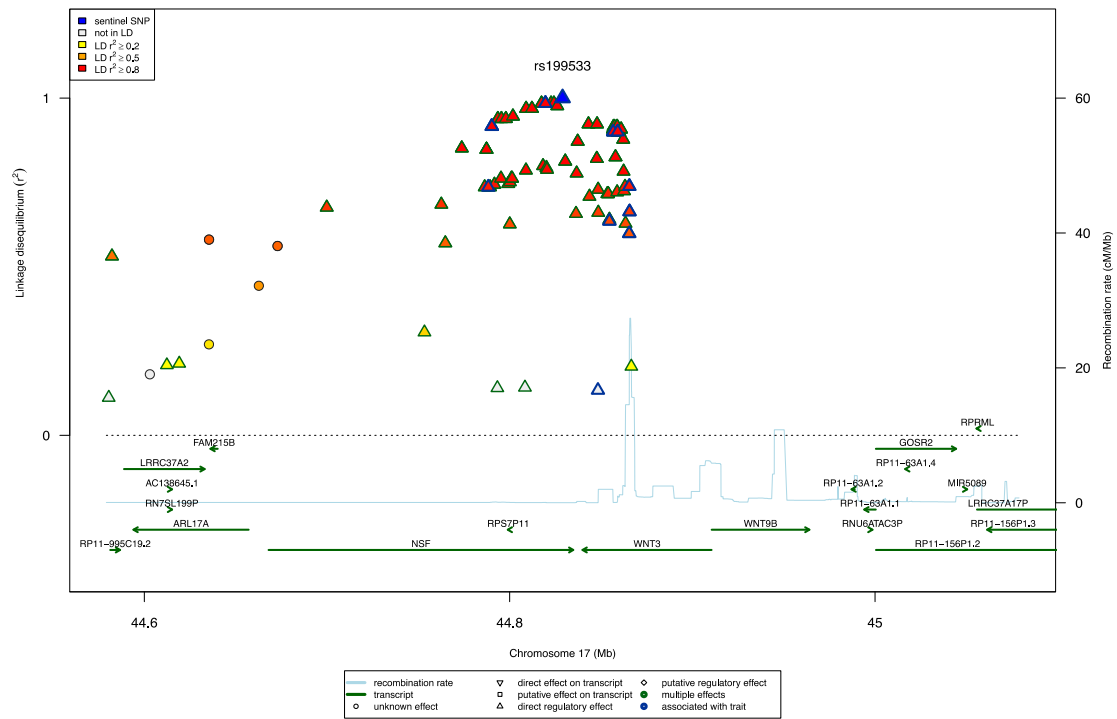
(d) over time is also illustrated.

Supplemental Figure 6. Line plots illustrating *RALB* gene expression in tau transgenic (red line) and wild-type mice (black line) from 2 to 18 months of age, across the (a) hippocampus, (b) cortex, and (c) cerebellum. Total tau pathology (d) over time is also illustrated.

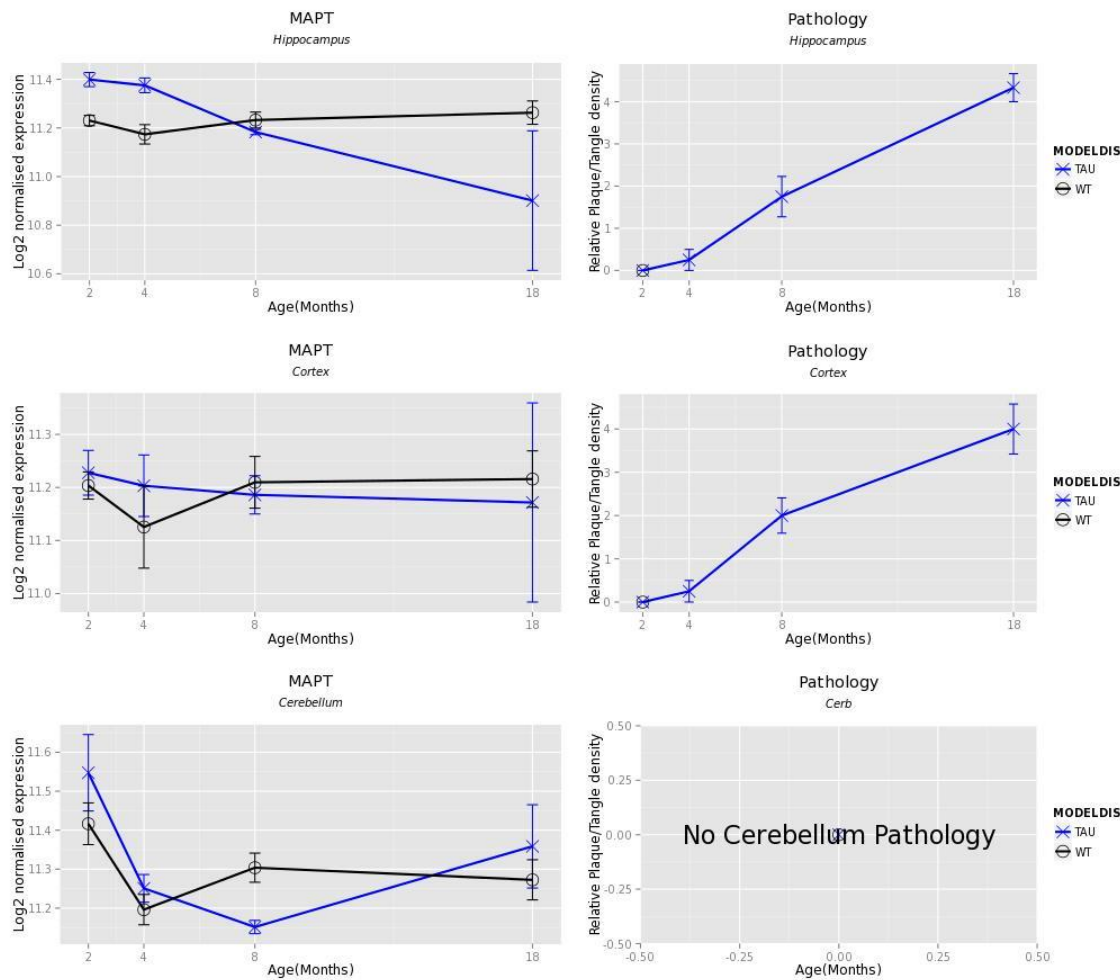
Supplemental Figure 1a



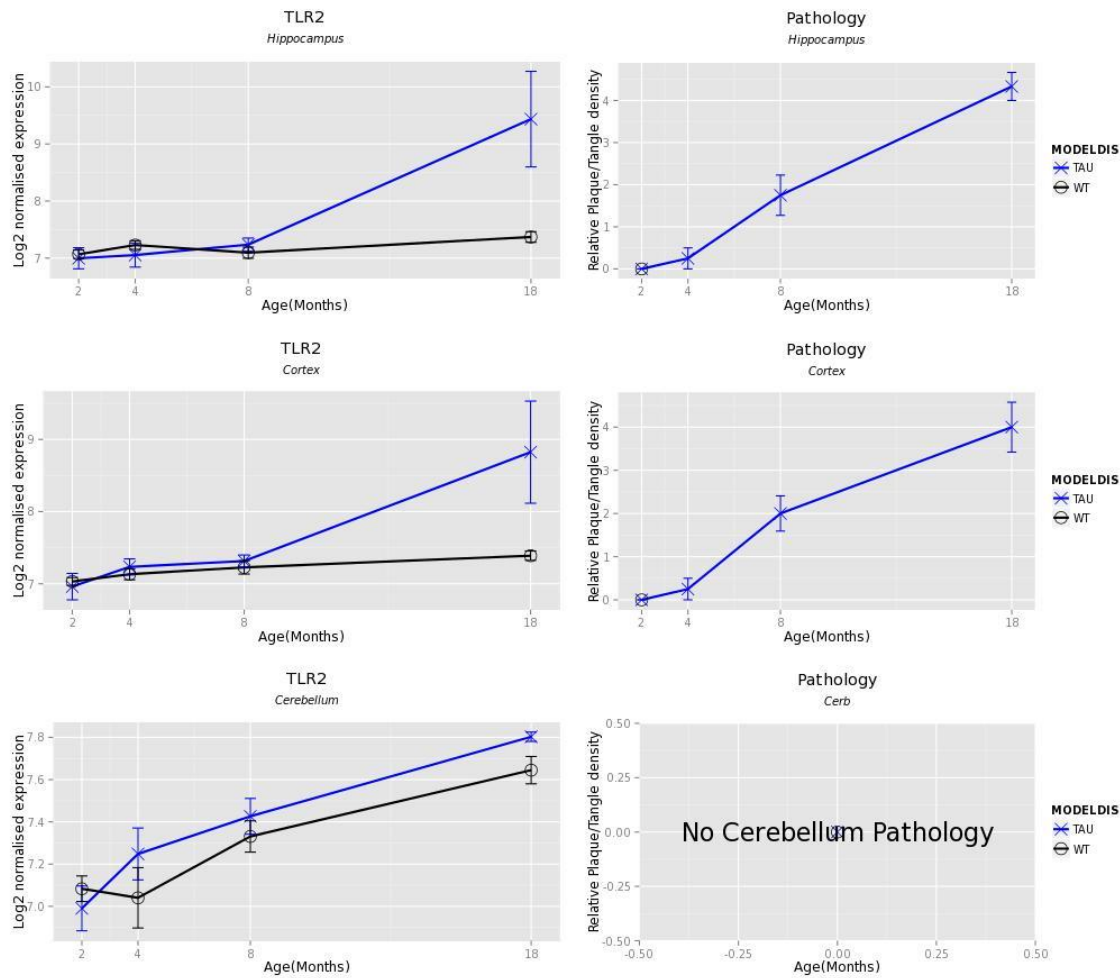
Supplemental Figure 1b



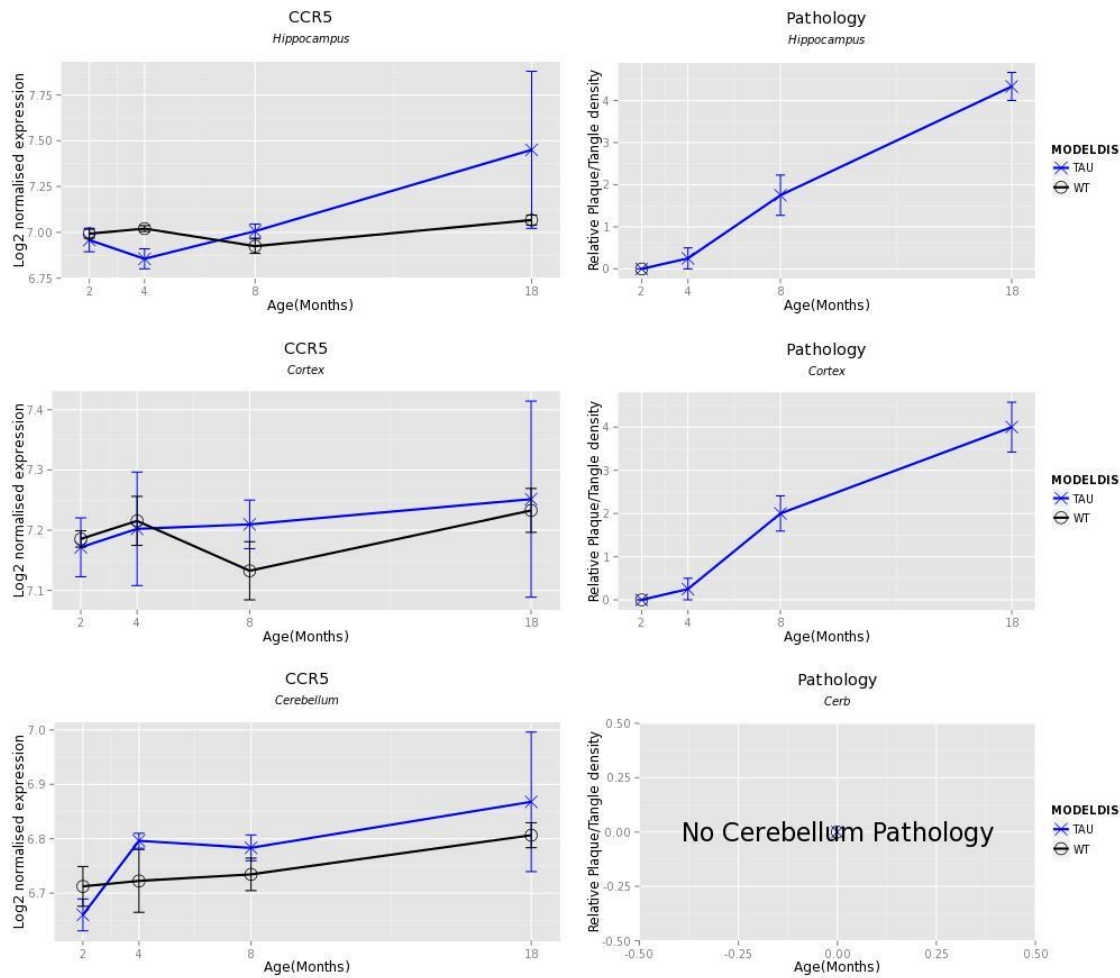
Supplemental Figure 2



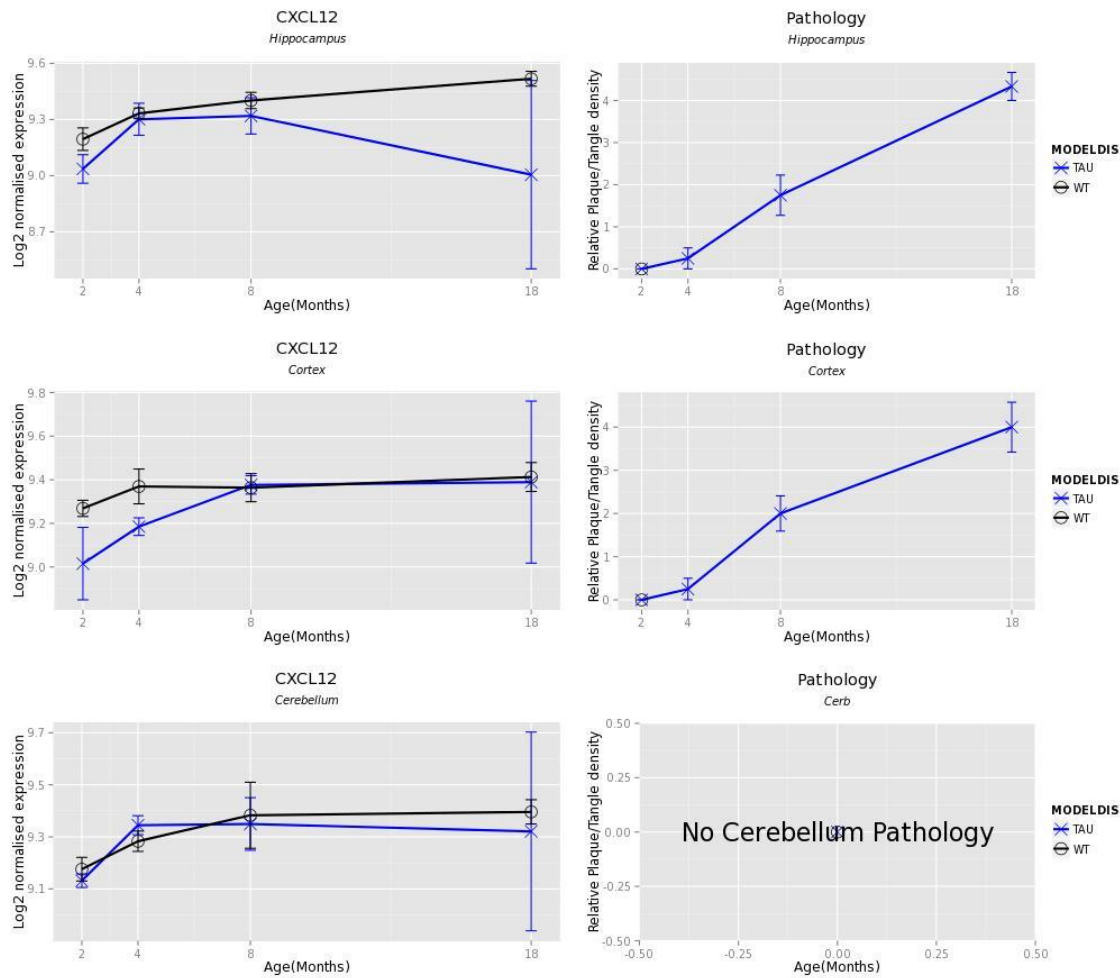
Supplemental Figure 3



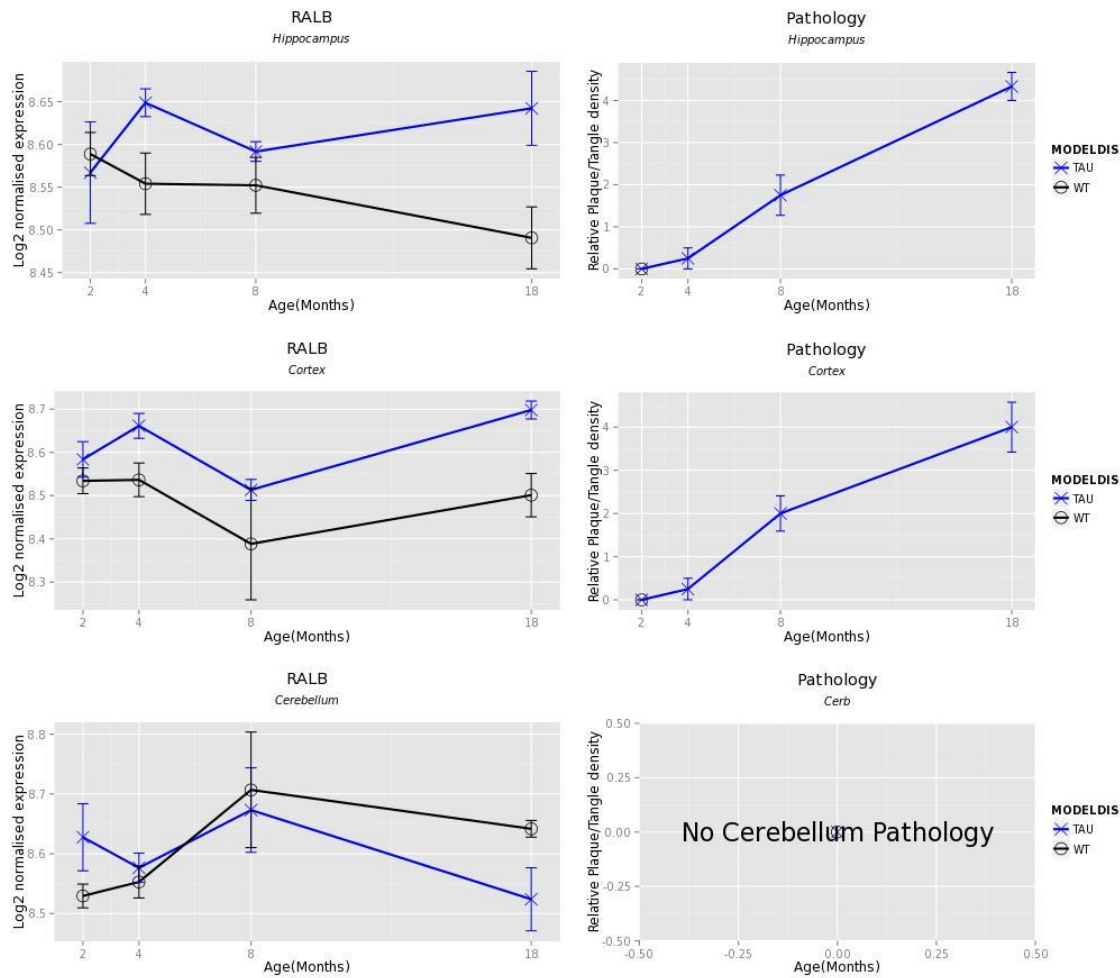
Supplemental Figure 4



Supplemental Figure 5



Supplemental Figure 6



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