# SEX DIFFERENCE IN CHI3L1 EXPRESSION LEVELS IN HUMAN BRAIN AGING AND IN ALZHEIMER'S DISEASE

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## ABSTRACT

**Introduction:** Several genetic sexual dimorphisms have been identified in animal and human brains, which may form a neural basis for sex-specific predisposition to neurological diseases. In the last years, clinical studies have observed that Alzheimer's disease (AD) disproportionately affects women compared with men. Chitinase-3-Like 1 protein (CHI3L1) has been frequently investigated in body fluids as a surrogate marker of neuroinflammation in AD and other neurological disorders. Nevertheless, the sex-related differences in CHI3L1 expression in the human brain has not yet been investigated. Here we aimed to evaluate the specificity of increase of CHI3L1 in five brain regions (cerebellum, dorsolateral prefrontal cortex, prefrontal cortex, hippocampus, and visual cortex) of male and female healthy controls during normal brain aging, as well as in AD patients.
**Methods**: We selected ten microarray datasets from NCBI, representing normal aging (n=1360) and AD (n=992), and stratified the brain specimens according to age, gender and brain region.
**Results**: The expression levels of CHI3L1 were correlated with age and gender. Healthy female brain specimens showed higher CHI3L1 expression than males. The expression differences between men and women were most obvious in older subjects. The expression analysis of CHI3L1 in the different brain regions of AD subjects also showed sex differences; females with AD had greater expression in the cerebellum than males. Notably, sex-associated CHI3L1 expression differences in hippocampus disappeared in AD.
**Conclusions**: These findings demonstrate that the expression of CHI3L1 in the brains of healthy subjects and AD patients is closely linked to age and sex, which was most obvious in the cerebellum. Further studies are needed to confirm our results.

KEY WORDS: chitinase; Alzheimer's disease; CHI3L1; YKL40; sex

ABBREVIATIONS: chitinase-3-like 1 protein (CHI3L1); non-demented healthy control subjects (NDHCS)**;** Alzheimer's disease (AD); Late Onset Alzheimer's disease (LOAD); Gene Expression Omnibus (GEO); formalin fixed, paraffin embedded (FFPE); prefrontal cortex (PFC); frontal cortex (FC); prefrontal cortex (DLPFC); visual cortex (VC); cerebellum (CB); Harvard Brain Tissue Resource Center (HBTRC); hippocampus (HPC); entorhinal cortex (EC); superior frontal cortex (SFC); post-central gyrus(PCGY); laser capture microscopy (LCM); superior frontal gyrus (SFGY); Significantly Different Expressed Genes (SDEG); MultiExperiment Viewer (MeV)

## INTRODUCTION

Neuroscience of sex differences is a growing branch of research. Being able to trace genetic differences, characterizing the brain as a function of sex, represents a challenge that scientific research has set itself as a recent goal using new technological advances. It has been shown that women tend to live longer than men and have notably lower death rates than men at all ages[1,2]. Possible reasons for these differences include genetic differences, hormones, and extrinsic factors such as lifestyle, health habits, exercise, and nutrition[3]. The effect of sex on age-related changes in brain cells represents an interesting starting point to explain the influence of sex on human aging. Several neurodegenerative diseases show sex differences in prevalence and/or outcome. For example, disease such as autism predominantly affects boys, Parkinson's disease is more common in men, multiple sclerosis and depression are more common in women, and so is Alzheimer's disease (AD)[4]. Yet another disease category with clear differences is inflammatory diseases[4]. Neuroinflammation has been identified as central in neurodegenerative processes and its control represents a challenge for neurobiology. Among the cells involved in neuroinflammatory processes, we have the microglia. This cell plays a crucial role in the onset and modulation of neuroinflammation and thus sex differences in microglial action could be linked to the differences observed in the susceptibility to neurodegenerative disease in men and women[5]. A recent study

has shown that in female mice the microglia are neuroprotective because they restrict the damage caused by acute focal cerebral ischemia[6]. It must be kept in mind that transformation of microglia to a reactive state is under genetic control and dysregulation may play a role in driving both neurodegenerative and neuroinflammatory diseases[7].

The discovery of microglia activation molecules represents a new strategy for the early diagnosis of neuroinflammatory and neurodegenerative diseases. Chitinase 3 like 1 (CHI3L1, also known YKL-40) is a secreted glycoprotein, encoded by the *CHI3L1* gene, which is expressed in microglia and astrocytes in association with neuroinflammation[8]. The real function of CHI3L1 is unknown, but it has been associated with several inflammatory diseases, as well as many cancers[9]. It has been frequently investigated in body fluids as a surrogate marker of neuroinflammation in AD[10,11], multiple sclerosis [12], ALS[13,14], neuro HIV[15], as well as in other neurological disorders[16]. However, sex-related differences in CHI3L1 expression in the human brain have not been deeply investigated. In 2016, our group found that there was a difference in the CHI3L1 expression in the brain biopsies of 19 females and 82 non-demented males[10]. Similar results were observed in Late Onset Alzheimer's disease (LOAD) patients. Our studies failed to include adequate numbers of males and females in order to allow us to test the hypothesis on gender differences in CHI3L1 expression.

Here we aimed to evaluate the specificity of increased CHI3L1 in five brain regions (cerebellum, dorsolateral prefrontal cortex, prefrontal cortex, hippocampus, and visual cortex) of 1360 non-demented healthy control during aging. In order to do that, we selected ten-microarray dataset from NCBI and stratified the brain biopsies in function of age, gender and brain regions. Furthermore, we analyzed the difference in the CHI3L1 expression levels in brain portions of 992 AD patients.

## MATERIALS AND METHODS

*Dataset collection*

The NCBI Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/) [17] was used to select transcriptome datasets to analyze CHI3L1 expression in several brain region. Mesh terms "Brain", "Cerebellum", "Prefrontal Cortex", "Alzheimer's Disease" and "Human" were used to identify potential datasets of interest. We sorted the obtained datasets by the number of samples (High to Low), age, gender, and for clinical data made available by the authors. Ten datasets (GSE28146, GSE33000, GSE36192, GSE36980, GSE44772, GSE48350, GSE5281, GSE53890, GSE84422 and GSE11882) were selected. A total of 1360 healthy subjects and 992 AD patients were analyzed. A full description of all dataset is available in the Supplemental Table 1.

The GSE28146 (platform GPL570), was composed of laser-captured hippocampal gray matter from FFPE (formalin fixed, paraffin embedded) hippocampal sections of 8 non-demented healthy control subjects (NDHCS) (6 male and 2 female) and 22 AD patients (6 male and 16 female) at varying stages of severity (incipient, moderate, severe)[18]. GSE33000 (platform GPL4372) was composed of postmortem prefrontal cortex (PFC) samples of 624 demented patients (n=310 AD, 135 male and 175 female) and NDHCS (n=157, 123 male and 34 female) with matched genotype and clinical data[19]. The GSE36192 (platform GPL6947) was composed of cerebellum and frontal cortex (FC) from 471 NDHCS (320 male and 151 female, 911 tissue samples in total)[20]. From the GSE36980 (platform GPL6244), we selected data from gray matter of frontal and temporal cortices and hippocampi derived from 79 postmortem brains, among which 32 cases were pathologically diagnosed as having AD (15 male and 17 female) and 47 NDHCS (22 male and 25 female)[21]. The GSE44772 (platform GPL4372) was composed of tissues from dorsolateral prefrontal cortex (DLPFC), visual cortex (VC) and cerebellum (CB) in brains of 387 LOAD patients (186 male and

201 female), and 303 NDHCS (246 male and 57 female), collected through the Harvard Brain Tissue Resource Center (HBTRC)[22]. From GSE48350 (platform GPL570), we selected data from 173 NDHCS (91 male and 82 female) and 80 AD patients (33 male and 47 female) from four brain regions: hippocampus (HPC), entorhinal cortex (EC), superior frontal cortex (SFC), post-central gyrus (PCGY)[23-27]. The GSE5281 (platform GPL570) was composed of tissue collected by laser capture microscopy (LCM) of 6 brain regions (EC, HPC, medial temporal gyrus, posterior cingulate, superior frontal gyrus and primary VC), 74 tissue from NDHCS and 87 from AD patients[28-30]. Regarding GSE53890 (platform GPL570), we sorted the data from 41 NDHCS brain (20 male and 21 female) (cortical grey matter dissected from the frontal pole) of 12 young (<40yr), 9 middle aged (40-70yr), 16 normal aged (70-94yr), and 4 extremely aged (95-106yr)[31]. From the dataset, GSE84422 (platform GPL570), we decided to sort the data of 102 brain, 28 from NDHCS (16 male and 12 female) and 74 from AD patients (all female). The brain regions included amygdala and nucleus accumbens[32]. GSE11882 (GPL570) was composed of samples of HPC, EC, superior frontal gyrus (SFGY), and PCGY across the lifespan of 58 (29 male and 29 female) NDHCS from 20-99 years old [23,33].

All subjects were stratified according to age and sex. Seven groups were obtained: young adult (18-35 years), adult (36-45 years), middle-age (46-65 years), senior (66-75 years), elderly (76-89 years), nonagenarian (90-99 years) and centenarian (>100 years)[34].

***Data processing and experimental design***

To process and identify Significantly Different Expressed Genes (SDEG) in all datasets, we used the MultiExperiment Viewer (MeV) software. In cases where multiple genetic probes had the same NCBI GeneID, we used those with the highest variance. The significance threshold level for all data sets was $p<0.05$. The genes with $p<0.05$ were identified as significantly differentially expressed

genes (SDEG) and selected for further analysis. For all datasets we performed a statistical analysis with GEO2R, applying a Benjamini & Hochberg (false discovery rate) to adjust P values for multiple comparisons [35-37].

### *Statistical analysis*

For statistical analysis, Prism 7 software (GraphPad Software, USA) was used. Based on Shapiro-Wilk test, almost all data were skewed, so nonparametric tests were used. Significant differences between groups were assessed using the Mann–Whitney U test, and Kruskal-Wallis test was performed to compare data between all groups followed by Dunn's post hoc test. Correlations were determined using Spearman's ρ correlation. All tests were two-sided and significance was determined at $P < 0.05$. The analysis of microarray data by Z-score transformation was used in order to allow the comparison of microarray data independent of the original hybridization intensities[38]. Raw intensity data for each experiment is log10 transformed and then used for the calculation of Z scores. Z scores are calculated by subtracting the overall average gene intensity (within a single experiment) from the raw intensity data for each gene, and dividing that result by the SD of all of the measured intensities, according to the formula:

$$\text{Z score (intensity G - mean intensity G1...Gn)/SDG1...Gn}$$

where G is any gene on the microarray and G1... Gn represent the aggregate measure of all of the genes.

## RESULTS

### *The CHI3L1 expression is related to sex and age*

The z-score analysis allowed us to merge the ten selected datasets, obtaining 1360 brain sections of NDHCS. We have stratified all the subjects selected according to age, obtaining seven categories:

young adult (18-35 years), adult (36-45 years), middle-age (46-65 years), senior (66-75 years), elderly (76-89 years), nonagenarian (90-99 years) and centenarian (> 100 years). Comparing all groups, we showed that CHI3L1 expression increased with age reaching a peak in the senior group, whereafter the expression level stabilized (Figure 1A) (Supplementary Table 1). The correlation analysis with age confirmed that CHI3L1 expression increased with age ($r=0.3943$, $p<0.0001$). We decided to divide the brain biopsies of the NDHCS according to sex, which resulted in data from 988 males and 487 females. The analysis of CHI3L1 expression obtained by comparing all brain specimens of the two sexes showed a significant increase in females brain biopsies compared to males ($p<0.0001$) (Figure 2A). Furthermore, for both genders, CHI3L1 expression level correlated positively with age (males $r=0.3873$ and $p<0.0001$; females $r=0.2410$ and $p<0.0001$) (Figure 2B/C). In light of these results, we decided to deepen our investigation by analyzing CHI3L1 expression according to sex in different age groups (Figure 3). A multiple comparisons analysis in men of different ages showed a higher CHI3L1 expression in young adults vs. most other age groups ($p<0.0001$) (Figure 3) (Supplementary Table 2A). In women, significant results were the comparison between the young adult vs. senior ($p<0.0001$), young adult vs. nonagenarian ($p=0.0059$), adult vs senior ($p=0.0039$), middle-age vs. senior ($p<0.0001$), middle-age vs. nonagenarian ($p=0.0005$), and senior vs. elderly ($p=0.0002$) age groups (Figure 3) (Supplementary Table 2B). Furthermore, we showed that between the age of 18 and 75 years, CHI3L1 expression was significantly higher in women than in men (in young adult $p = 0.0094$; in adult $p = 0.020$; in middle-age $p = 0.023$; in senior $p <0.0001$) (Figure 3). No significant differences between men and women were detected in the elderly, nonagenarians and centenarians. The most significant difference between male (n=212) and females (n=98) was identified in senior subjects, aged between 66 and 75 years (Figure 3) ($p<0.0001$). This data was consistent with the results obtained

during the analysis of expression levels independently of sex (Figure 1), in which we showed that the CHI3L1 expression was the highest in senior subjects.

### *The hippocampus of non-demented healthy senior subjects presents high expression levels of CHI3L1 according to the sex*

Our previous results showed that senior subjects presented the highest expression levels of CHI3L1, and a highly significant difference between the two sexes. A more in-depth analysis of the different brain regions of senior subjects (n=309) showed that CHI3L1 was highly expressed in the hippocampus compared to the CB, DLPFC, PFC and VC (Figure 4A) (Supplementary Table 3A). In addition to carrying out the analysis according to the sex, we showed significant differences CHI3L1 expression in the CB ($p = 0.0089$), in the hippocampus ($p = 0.0025$) and in the VC ($p = 0.0132$) of women compared with men (Figure 4B). No significant difference was observed in the DLPFC and PFC between men and women in the senior group (Figure 4B). A multiple comparisons analysis showed that CHI3L1 expression was the highest expression in the hippocampus of senior men compared with all other brain regions and age and gender groups (Supplementary Table 3B). In women, CHI3L1 expression was higher in hippocampus vs. DLPFC ($p = 0.02$), and vs. PFC ($p <0.0001$) (Supplementary Table 3C).

### *Sex-related CHI3L1 expression differences in the AD brain.*

In our previous work, we showed that the CHI3L1 expression was significantly higher in AD subjects than NDHCS. In addition, we had highlighted a difference in expression even between male and female subjects[10]. In the current dataset, CHI3L1 expression was higher in AD subjects (n = 992) than in NDHCS (n = 1329) (Figure 5A) ($p <0.0001$). Significant differences were also observed in different brain regions (CB $p <0.0001$; DLPFC $p <0.0001$; PFC $p <0.0001$; HPC $p = 0.046$; VC $p <0.0001$) (Figure 5B). A multiple comparisons analysis of CHI3L1 expression in different AD brain

regions, showed higher expression in VC compared with CB (p=0.005), PFC (p<0.0001) and HPC (p=0.0004)(Figure 5B)(Supplementary Table 4A). Women with AD (n=567) had higher CHI3L1 expression levels then men (n=425, p = 0.03, Figure 6A). A more detailed investigation of sex-related differences in CHI3L1 expression in the different AD brain regions showed that only the CB had higher expression in women compared with men (p <0.0028) (Figure 6B). No significant differences were found in the remaining AD brain regions analyzed. Furthermore, a multiple comparison analysis of AD brain regions according to sex showed no significant differences in CHI3L1 expression between the different brain regions (Figure 6)(Supplementary Table 4B). In women with AD, we showed that CHI3L1 expression was significantly higher in VC compared with PFC (p=0.007) and HPC (P=0.005) (Figure 6)(Supplementary Table 4C).

**DISCUSSION**

In this study, we hypothesized that sex could influence CHI3L1 mRNA expression during brain aging, as well as in AD. To address our hypothesis, we analyzed ten microarray datasets available on GEODataSet, for a total of 1360 brain specimens of NDHCS (988 men and 487 women), and 992 of AD patients (425 men and 567 women). Subject stratification according to age showed that CHI3L1 expression was closely related to aging, and the major differences were seen when comparing young adult subjects (years 18-35) with senior women (years 66-75) and nonagenarian men (years 90-99). Other relevant data were obtained when analyzing CHI3L1 expression in the different brain regions of senior subjects. We showed higher CHI3L1 expression in the CB, in the HPC, and in the VC in women compared with men. In AD brains, CHI3L1 expression was higher than in NDHCS. Moreover, women with AD exhibited higher levels of CHI3L1 compared to men in the CB portion. All these results demonstrate for the first time that CHI3L1 expression in the brain

increases with age, is higher in women than in men and is increased in AD, particularly so in women with AD.

In the last decade, several researchers have tried to explain the role of CHI3L1 in the human body. There is evidence that this molecule is closely related to the inflammatory processes and its activity is connected to degenerative phenomena[39]. The structure analysis revealed that this molecule lacks enzymatic activity but its carbohydrate-binding domain (CBD) is still functional. The ability to bind carbohydrate residues means that this molecule with evolution has found new targets in addition to chitin, its natural binding molecule[40]. It has been shown that modulation of this protein is involved in cytoskeleton remodeling during monocyte maturation and/or activation. Its potential functions in the immune system have been extensively elucidated during both inflammation and carcinogenesis[41]. Its expression is often linked to the line of innate immunity and in particular to all monocyte-derived cells such as alveolar macrophages[42], macrophages M1 and M2[43], dendritic cells[44], osteoclasts[45], astrocytes[8,46] and microglia[47]. In the brain, CHI3L1 is overexpressed in several neurological disorders such as neuro HIV[15], encephalitis[48], stroke[49], ALS[13], schizophrenia[50], MS[51] and AD[52]. The CHI3L1 cellular localization in the brain is purely in the white matter, and in particular in astrocytes and microglia. These two cells play a very relevant role in degenerative processes and in brain aging[7,53]. The changes that occur during normal brain aging are not well understood.

In this paper, we showed that the CHI3L1 expression levels were increased in women compared with men during aging and reached a peak in senior subjects in the HPC, CB, and VC brain regions of NDHCS. Although sexual differentiation of the brain has been extensively investigated, the study of sex differences in the brain's resident immune cells has been largely neglected until recently[54]. There is new evidence of an imbalance between the amount of glia in women compared with men[6].

To date, there are no answers regarding the variation in the amount of glia in the brain during aging and in terms of sex. The HPC, CR and VC increase their portion of glial cells during aging (ref?). Indeed, it has been shown that there are age- and gender-related differences in the number of astrocytes and microglial cells in HPC of mice. Older female mice have ~20% more glial cells than young females, and females at all ages have 25–40% more glial cells than age-matched males [55]. Regarding the CB, it was demonstrated that during aging, there is a progressive loss of cerebellar Purkinje neurons and an increase in cerebellar behavioral deficits[56]. In a recent papers, it has been showed that microglia and astrocytes show alterations in gene expression in the aging brain, and these changes vary by brain region[53,57]. There is not enough information about pathological changes in the VC during normal aging. In AD, the VC shows an increase in Aβ42 deposits, accompanied by the increase in local sites of astrocytes and microglia[58]. However, the presence of Aβ42 in the VC and the role played in vision loss, related to normal aging, have not been still enough described [59]. Our study could confirm the presence of microglia and astrocytes in the VC during aging according to the expression of CHI3L1 closely related to the inflammatory process and both with these two types of cells.

Include a paragraph on strengths and limitations of the study + the need for further studies?

Our analysis confirmed that CHI3L1 is more expressed in AD than in healthy subjects. Furthermore, we found a significant difference in CHI3L1 expression levels in CB of AD patients according to the sex. Existing a large literature on structural and functional studies of the CB modification in AD[60,61]. It has been shown that there is an acceleration in age-related cerebral atrophy in AD [62] and this is accompanied by an increase in activated glia[63]. The increase in levels of CHI3L1 in the CB of women compared with men with AD could be explained by the greater physiological presence of glia in females. In light of this, we could hypothesize that during the

development of AD, there is an increase in the number of glial cells in the brain that disproportionate in both sexes. This unbalance in the glia percent in the AD brain sex-related, could be reduced as the disease progresses.

## CONCLUSIONS

CHI3L1 is an extremely interesting molecule in degenerative and inflammatory processes. Although it is an ancestral molecule, it seems to continue to play a role in the human immune system although its precise function(s) remain elusive. The presence of polymorphic sites demonstrates its susceptibility to evolution[64]. Our findings of sex-, age- and disease-related differences in CHI3L1 expression in the brain provide further support for a functional role of the protein in neuroinflammatory and –degenerative processes.

FIGURES LEGENDS

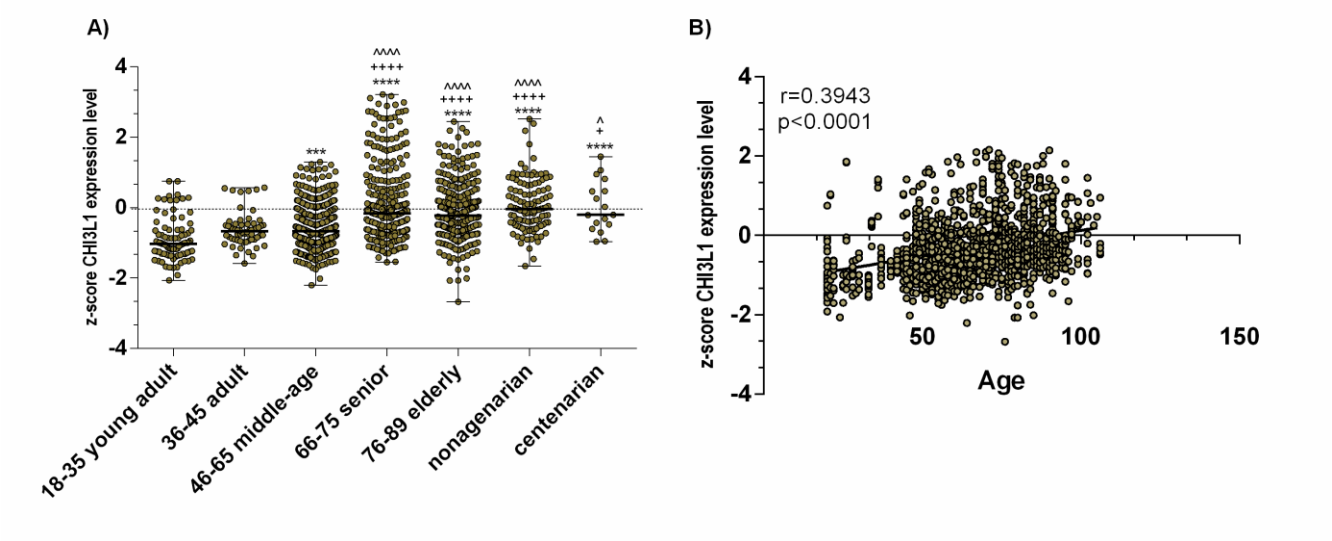


**Figure 1: The brain of NDHCS express different levels of CHI3L1 during the aging**

The analysis of CHI3L1 expression levels in brain biopsies of NDHCS showed a gradual increase with aging until reaching a peak in the senior and nonagenarian subjects (A). Expression levels were positively correlated with the age of the subjects analyzed (r=0.3943, p<0.0001)(B). Data are expressed as z-score intensity expression levels and presented as vertical scatter dot plots. P values <0.05 were considered to be statistically significant (*,^,+p<0.05; **,^^,++p<0.005;***,^^^,+++p<0.0005; ****,^^^^,++++p<0.00005).

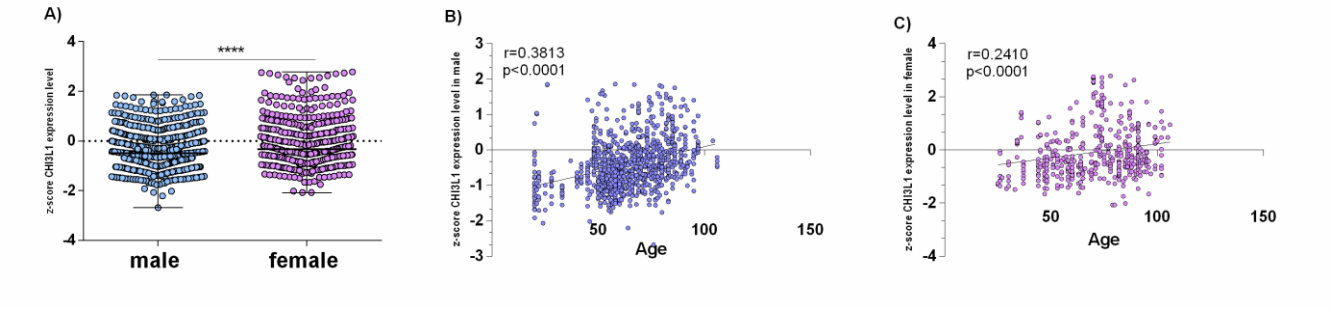


**Figure 2: The CHI3L1 expression in healthy brain is sex linked**

The analysis of CHI3L1 expression levels obtained by comparing the all brain specimens of the two sexes showed a significant increase in female vs. male brains (p<0.0001)(A). For both sexes, the CHI3L1 expression levels correlated positively with age (males r=0.3873 and p<0.0001; females r=0.2410 and p<0.0001)(B). Data are expressed as z-score intensity expression levels and presented as vertical scatter dot plots. P values <0.05 were considered to be statistically significant (*p<0.05; **p<0.005;***p<0.0005; ****p<0.00005).

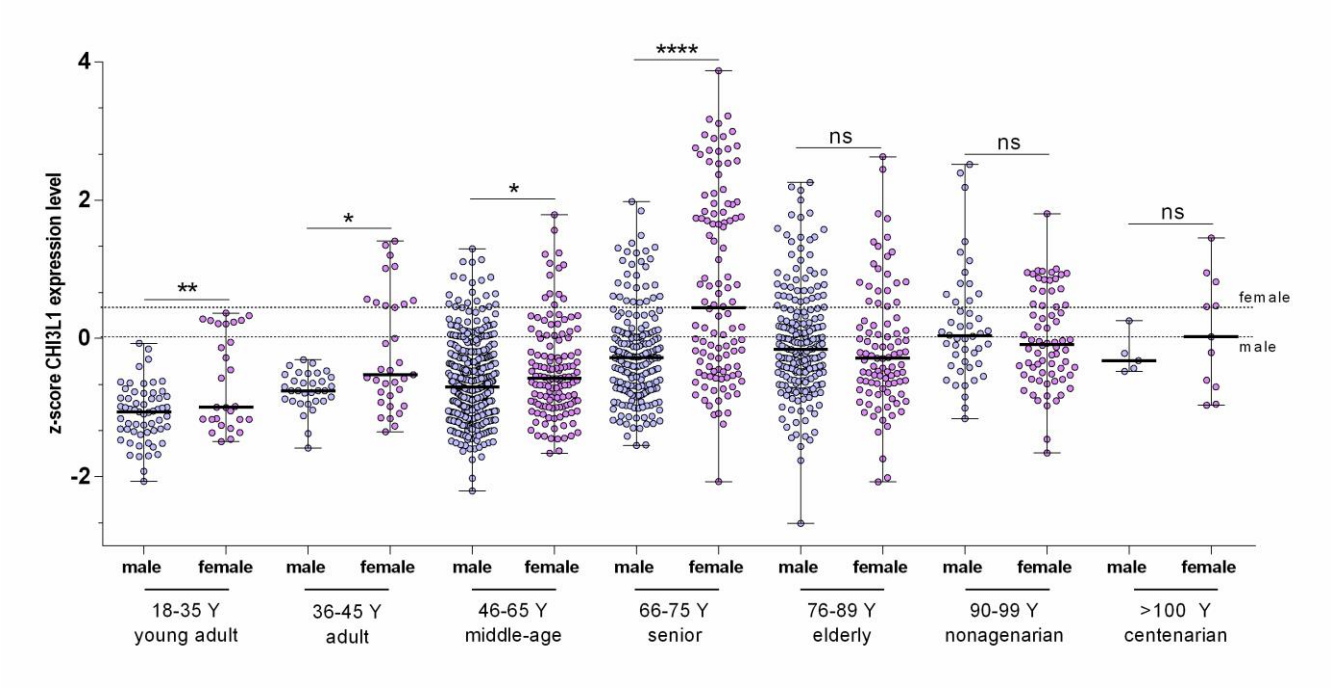


**Figure 3: Healthy brains of senior subjects express high levels of CHI3L1**

In the first part of adulthood, between the ages of 18 and 75, CHI3L1 expression levels were significantly higher in women than in men (p = 0.0002; adult p = 0.01; middle-age p = 0.001; senior p <0.0001). No significant difference between men and women was seen in the elderly, nonagenarians and centenarians. Data are expressed as z-score intensity expression levels and presented as vertical scatter dot plots. P values <0.05 were considered to be statistically significant (*p<0.05; **p<0.005;***p<0.0005; ****p<0.00005).

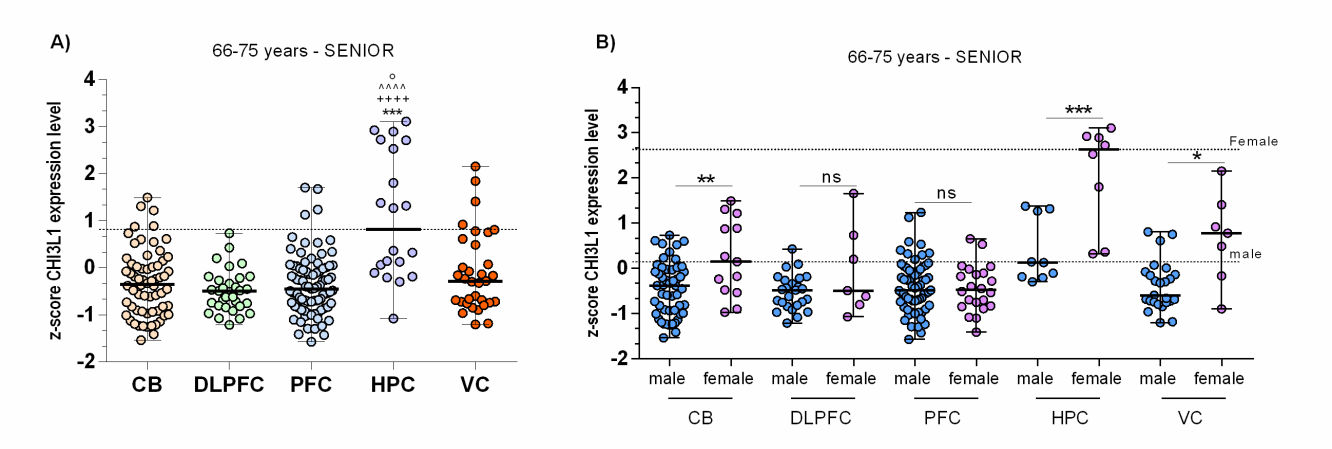


**Figure 4: Senior HPC of NDHCS express high levels of CHI3L1 according to the sex**

The analysis of the different brain regions of senior subjects (n=309) showed that CHI3L1 expression was higher in the HPC compared with the CB (p<0.0001), DLPFC (p<0.0001), PFC (p<0.0001) and VC (p<0.0001) (p=0.0116)(A). There were also significant differences in CHI3L1 expression levels in the CB (p = 0.0089), in the HPC (p = 0.0025) and in the VC (p = 0.0132) when

comparing women and men (B). Data are expressed as z-score intensity expression levels and presented as vertical scatter dot plots. P values <0.05 were considered to be statistically significant (*p<0.05; **p<0.005;***p<0.0005; ****p<0.00005).

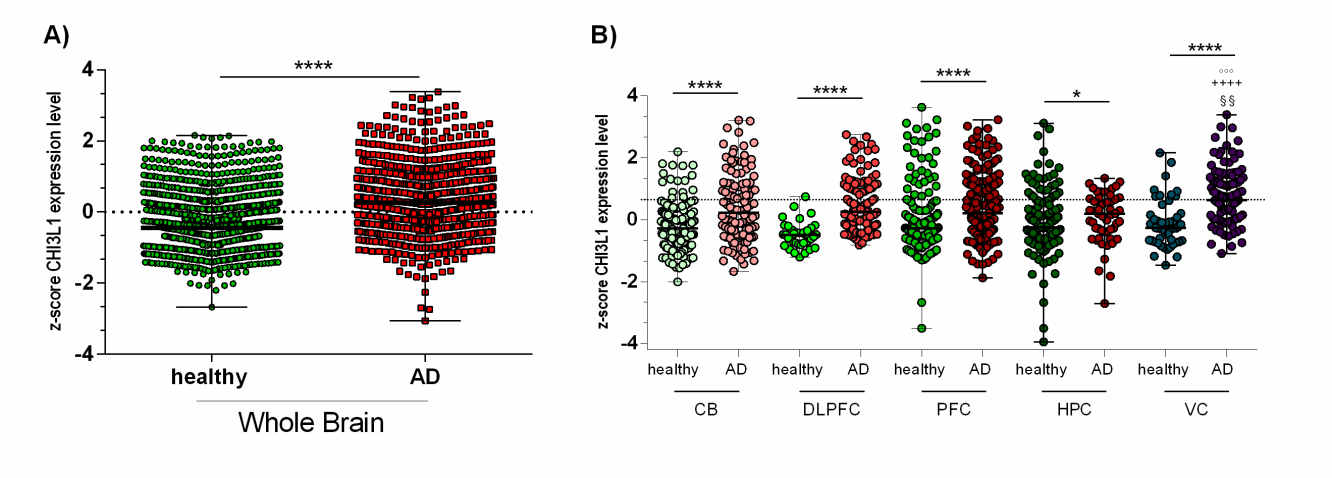


**Figure 5: CHI3L1 expression levels are higher in AD compared with NDHCS brains**

CHI3L1 expression is significantly higher in AD compared with NDHCS brains (A). It is also possible to notice that CHI3L1 expression is different in different AD brain regions (p <0.0001 for CB; p <0.0001for DLPFC; p <0.0001for PFC; p = 0.046 for HPC; p <0.0001 for VC )(B). Data are expressed as z-score intensity expression levels and presented as vertical scatter dot plots. P values <0.05 were considered to be statistically significant (*p<0.05; **p<0.005;***p<0.0005; ****p<0.00005).

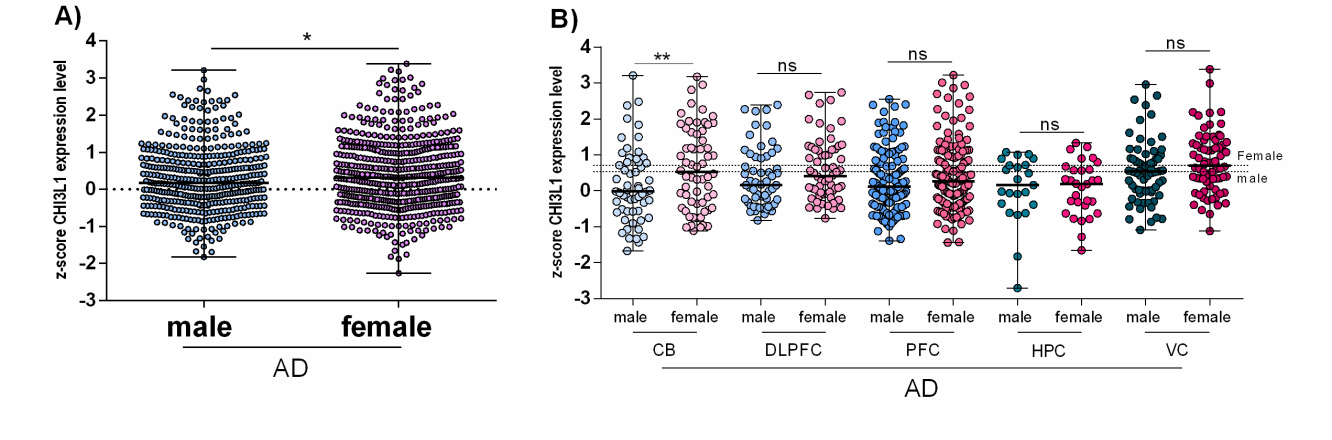


**Figure 6: CB of female AD patients express significantly higher levels of CHI3L1 compared with male CB**

CHI3L1 expression in AD brains sorted according to sex, shows higher levels in female than in male brains (p = 0.04)(A). CHI3L1 expression in CB was higher in women compared with men (p <0.0028)(B). Data are expressed as z-score intensity expression levels and presented as vertical scatter dot plots. P values <0.05 were considered to be statistically significant (*p<0.05; **p<0.005;***p<0.0005; ****p<0.00005).

**Supplementary Table 1: CHI3L1 expression in NDHCS with different age**
Multiple comparisons analysis of CHI3L1 expression levels in brain biopsies of NDHCS with different age.

**Supplementary Table 2: CHI3L1 expression in NDHCS with different age according to the sex**
Multiple comparisons analysis of CHI3L1 expression levels in brain biopsies of NDHCS with different age according to sex.

**Supplementary Table 3: CHI3L1 expression in brain portions of non-demented healthy senior subjects**
Multiple comparisons analysis of CHI3L1 expression levels in in brain portions of non-demented healthy senior subjects according to sex.

**Supplementary Table 4: CHI3L1 expression levels in brain portions of AD subjects**
Multiple comparisons analysis of CHI3L1 expression levels in brain portions of AD subjects according to sex.

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