Alzheimer's disease is a TH17 related autoimmune disorder against misfolded beta amyloid

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Abstract

Alzheimer's disease is a common neurodegenerative disease. However, the exact pathogenesis of Alzheimer's disease is still unknown. There were several disease mechanisms proposed such as Tau hypothesis and amyloid hypothesis. However, there are observations challenging the above two hypothesis. Here, I provide reasons for the amyloid-immune hypothesis for the actual cause of Alzheimer's disease. In addition, TH17 related autoimmune reaction contributes to the disease pathogenesis. By microarray analysis of peripheral blood mononuclear cells, we can see that many TH17 immunity related molecules are up-regulated after the onset of Alzheimer's disease. After knowing the disease pathogenesis, we can develop new therapeutic strategies to prevent or treat the detrimental neurodegenerative disorder.

About the author

Wan-Jiung Hu is a MD PhD. His former name is Wan-Chung Hu. His MD degree was awarded from National Taiwan University. His PhD degree was awarded from Vaccine science track of Department of International Health of Johns Hopkins University. His PhD thesis was using microarray to identify the host immunological pathway after malaria infection. His first first-author paper: “Common and divergent immune response signaling pathways discovered in peripheral blood mononuclear cell gene expression patterns in presymptomatic and clinically apparent malaria” is published in Infection and Immunity in 2006 October. Thus, he first proposed the THαβ immunity which is host immunity against viruses and certain protozoa. A subsequent paper in 2008 called it TH9 immunity. He was trained as a neurology resident in Department of Neurology of Taipei Mackay Memorial Hospital of Taiwan. Currently, he is doing postdoc research in Academia Sinica, Taiwan. His current research topic is cancer immunotherapy. The author would like to publish this manuscript. If journal editors are interested in this paper, please feel free to contact me.

Introduction

Alzheimer’s disease is a very common neurodegenerative disorder. The risk of Alzheimer’s disease is higher in older population. Even though Alzheimer’s disease is very common, the exact pathogenesis is still unknown. Several hypotheses were proposed for the cause of Alzheimer’s disease. First, there was tau hypothesis. Tau protein is important in normal neuron function. Abnormal hyperphosphorylated Tau proteins are found in Alzheimer’s disease. Thus, several researchers proposed that abnormal hyperphosphorylated Tau accumulation is the cause of Alzheimer’s disease. However, abnormal Tau is not specific to Alzheimer’s disease. In addition, many healthy people without Alzheimer’s disease can be found Tau tangles in brain tissue during their autopsy. Thus, Tau hypothesis is not likely to be true. Second, there is amyloid hypothesis. Amyloid beta accumulation was found in extracellular cortex area in Alzheimer’s disease. Thus, misfolded amyloid beta fibrils are thought to be the cause of Alzheimer’s disorder. Amyloid beta accumulation is specific to Alzheimer’s disease. In addition, amyloid beta can induce Tau hyperphosphorylation. Thus, amyloid beta fibrils are related to the pathogenesis of Alzheimer’s disease. However, vaccine made of amyloid beta cannot prevent Alzheimer’s disease in clinical trials even the vaccine can completely clear out amyloid beta fibrils. Here, I will support a new hypothesis: amyloid-immune hypothesis. Host autoimmunity induced by misfolded amyloid beta accumulation is the main cause of Alzheimer’s disease. By using microarray analysis of PBMCs from Alzheimer’s disease patients, we can find out that TH17 immunological pathway is up-regulated. In this study, I

propose that Alzheimer's disease is a TH17 related autoimmune disorder.

Material and methods

Microarray dataset

According to Dr. C.R. Scherzer's research in PNAS 2007, he collected total RNA from whole blood in several neurodegenerative disorders including Alzheimer's disease and healthy controls. His dataset is available in Gene Expression Omnibus (GEO) www.ncbi.nlm.nih.gov/geo (assession number GSE 6613). Dr. Scherzer used the dataset to study white blood cell gene expressions in early Parkinson disease compared to those in healthy controls and in other neurodegenerative disorders. In this study, I perform further analysis to study leukocyte gene expression profiles of Alzheimer's disease compared to those of healthy controls.

Statistical analysis

RMA express software(UC Berkeley, Board Institute) is used to do normalization and to rule out the outliners of the above dataset. I rule out the potential outliners of samples due to the following criteria:
1. Remove samples which have strong deviation in NUSE plot
2. Remove samples which have broad spectrum in RLE value plot
3. Remove samples which have strong deviation in RLE-NUSE mutiplot
4. Remove samples which exceed 99% line in RLE-NUSE T2 plot

Originally, there are 23 Alzheimer's disease samples and 22 healthy controls in the GSE6613 dataset. After the analysis of RMA express, we select 20 Alzheimer's disease and 19 healthy controls. We remove GSE153463, GSE153464, GSE153474, GSE153479, GSE153497, and GSE153508 due to RNA express analysis. Then, we use Genespring X to do the microarray significance analysis. Fold change >1.1 with P value <0.05 with no correction in FDR are used to compare Alzheimer's disease to healthy controls. Finally, we find out 2993 significantly expressed genes. From the significant genelist, I pick out protein processing and immune-related genes.

Validation by RT-PCR

Since this study is a secondary dataset analysis, I don't have samples in hand to do wet bench validation such as RT-PCR. However, in Dr. Scherzer's paper, he performed

RT-PCR to confirm his result of microarray experiment by using RT-PCR. He found that the gene ST13, a HSP70 cofactor, is down-regulated in Parkinsonism compared to that in Healthy control due to microarray analysis. Then, he used quantitative real-time PCR assays based on precise fluorogenic 5' nuclease chemistry in a large set of 39 Parkinsonism patients and 12 age-, sex-, and blood count- matched healthy controls. He used the housekeeping gene glyceraldehydes-3-phosphate dehydrogenase to control for input RNA and the comparative threshold cycle method for analysis. The RT-PCR results confirmed that ST13 is lower in Parkinsonism patients. Thus, it states that the microarray platform of Dr. Scherzer's experiments is valid and reliable.

Results

Sample selection from RNA express analysis

We use RNA express to draw several analytic plots to do the sample selection. We first look at the normal healthy control sample sets. According to NUSE values plot by array, sample GSM153479, GSM153497, and GSM153508 are removed due to board variation. According to RLE values plot by array, sample GSM153508 should be removed due to great variation. Based on RLE-NUSE multiplot, GSM153508 should be removed. Based on RLE-NUSE T2 plot, GSM153479, GSM153497, and GSM153508 should be removed. Finally, we remove the above three samples. Then, we look at the Alzheimer's disease sample sets. According to NUSE values boxplot by array, sample GSM153474 should be removed due to large deviation. According to RLE values boxplot, sample GSM153463 and GSM153474 should be removed. Based on RLE-NUSE multiplot, sample GSM153463, GSM153464, and GSM153474 should be removed. Based on RLE-NUSE T2 plot, GSM153463, GSM153464, and GSM153474 should be removed. Then, we remove the above three samples from dataset.

Up-regulation of heat shock proteins in Alzheimer's disease

According to the microarray analysis, we found that many heat shock protein genes are up-regulated after Alzheimer's disease. This confirms our previous hypothesis. Although certain and limited HSP40 and HSP27 are mid-moderate down-regulated, majority of HSP60s and HSP70s are up-regulated in Alzheimer's disease.(Table1). HSP60s and HSP70s are major heat shock proteins which activate TLR2 and TLR4 to initiate TH17 immunity. In addition, other molecular chaperons are significantly expressed after Alzheimer's disease. Cyclophilins are all up-regulated and FK506

binding proteins are mainly down-regulated in Alzheimer's disease.(Table 2 and Table3) Cyclophilins and FK506 binding proteins are peptidylprolyl isomerases which play important roles in antigen processing during immune response initiation. These isomerases are target of immunosuppressants: cyclosporine and FK506. Mainly cyclophilins tend to activate immune response and FK506 binding proteins tend to down-regulate immune response. In addition, we found that TLR1,2,8 are up-regulated after Alzheimer's disease. (Table4). TLR1 and TLR2 are toll-like receptors which initiate TH17 immunity against extracellular bacteria. It is worth noting that TLR2 is the receptor for heat shock protein. Although TLR8 could react to single strand RNA in certain studies, TLR8's function can be related to the suppression of Treg cells and the activation of Th17 related neutrophils. Our findings suggest that immune response can be up-regulated by these molecular chaperons via TLRs, especially heat shock proteins, for TH17 immunity in Alzheimer's disease.

Up-regulation of protein degradation genes in Alzheimer's disease

In our microarray analysis, we found majority of proteasomes and ubiqutin-related genes are up-regulated in Alzheimer's disease(Table 5 and Table 6). It is interesting to find out that proteasome activators are mainly up-regulated and proteasome inhibitors are down-regulated after Alzheimer's disease. Majority of ubiqutin-related genes are also significantly over-expressed such as ubiqutin protein ligases, ubiqutin specific peptidases, and ubiqutin conjugating enzymes. Proteasomes and ubiqutins are important in protein degradation machinery. They are also important in antigen processing step during immune response in cells. Since Alzheimer's disease is related to the accumulation of misfiled beta amyloid protein, it is very reasonable that these protein degradation machinery are up-regulated to deal with these overloaded beta amyloid. In our analysis, we also found that many MHC related genes are up-regulated after Alzheimer's disease.(Table 7). MHC related genes are for antigen presentation for B cells and T cells. In our study, we found majority of antigen processing and presentation genes are activated during Alzheimer's disease.

Up-regulation of TH17 immunity related genes in Alzheimer's disease

Based on this study, many TH17 immunity related genes are up-regulated during Alzheimer's disease. First of all, many general immune response genes are up-regulated including transcription factors ETS2 and FOS and TRAF family member-associated NFKB activator and NFIL3 and leukocyte immunoglobin-like receptors and IL-18 receptor accessory protein and several chemokine genes as wells

as many differentially regulated CD molecules and integrins. (Table 8) The immunosuppressant TGF betas well as Treg transcription factor Foxhead box P3 (FOXP3) is down-regulated in Alzheimer's disease. Majority of anti-inflammation genes: apoliproproteins are also down-regulated. This suggests that immune response is initiated in Alzheimer's disease.

Most important of all, many TH17 mediators are up-regulated in Alzheimer's disease. (Table 9) Important TH17 cytokines are up-regulated including IL-6 and IL-8. Interleukin 8 receptor and GM-CSF receptor are also up-regulated as well. Interleukin 1 receptor antagonist and IL-1 receptor accessory proteins are also up-regulated. IL-1 is an important immune mediator in TH17 immunity. There are opposite directions for certain TH2 receptors: IL-4 receptor and IL-13 receptor are up-regulated, but IL-9 receptor is down-regulated. Thus, there is no net up-regulated direction for TH2 pathway. Most important of all, key TH2 cytokines including IL-5 and IL-13 are down-regulated in Alzheimer's disease. It is interesting to find out that IFNg receptor and IL-10 receptor are both up-regulated in Alzheimer's disease. IFNg receptor signaling and IL-10 receptor signaling can antagonize each other. In addition, the key THαβ related gene (IL-27 receptor) is down-regulated. The master THαβ transcription factor IRF5, which can be activated by virus induced TLR7, is down-regulated after Alzheimer's disease. In addition, the transcription factor IRF2, which can interfere with the IFNα/β inducing IRF1, is up-regulated in Alzheimer's disease. Besides, many important interferon alpha induced genes are down-regulated such as IFI27, OAS2, and OASL. Majority of another key TH17 cytokine related molecule: TNFα and TNFα receptor family genes are up-regulated. And, key transcription factors for initiating TH17 immunity are activated including CEBPD and CEBPB. IL-6, IL-21, and IL-23, these TH17 cytokines, activate signaling transduction pathways to initiate TH17 immune response via JAK2 and TYK2. It is interesting to find out the above two genes are also up-regulated in Alzheimer's disease.

TH17 is driven by two important cytokines: TGF beta and IL-6. IL-6 is up-regulated in Alzheimer's disease. Although TGF beta is not activated, TGF beta receptor is up-regulated in Alzheimer's disease. In addition, the whole TGF beta signaling is activated. The key R-SMAD for developing TH17 immunity is SMAD2 with its co-SMAD, SMAD4. Both SMAD2 and SMAD4 are up-regulated after Alzheimer's disease. Besides, the inhibitory SMAD molecule: SMAD6 is down-regulated in Alzheimer's disease. Thus, TGF beta signaling is up-regulated in Alzheimer's disease. TGF beta signaling is involved in not only TH17 pathway but also Treg pathway. However, the key transcription factor for Treg: FOXP3 is down-regulated in

Alzheimer's disease. Thus, Treg pathway is not activated after Alzheimer's disease. Since TGF beta signaling and IL-6 signaling are activated, TH17 immunity is initiated in Alzheimer's disease.

Many downstream TH17 effector molecules are also activated in Alzheimer's disease. (Table 10) These include cathepsin genes, S100 calcium binding proteins, SERPINB1, granulysins, FCER1G, FCGR2C, FCGRT, C-type lectin, ferritin, and arachidonate 5-lipoxygenase. However, complement related genes are differentially regulated. Cathepsins are important in phagocytosis of bacteria. S100 calcium binding proteins are neutrophil chemoattractants. SERPINB1 is neutrophil survival factor. Granulysins, secreted from T cells, can attack gram positive or negative bacteria. FCER1G and FCGR2C are co-expressed on granulocytes such as neutrophils to mediate phagocytosis. C-type lectins can bind to extracellular bacteria. Ferritin can bind to iron to deprive this essential nutrient for bacteria. Arachidonate 5-lipoxygenase catalysis the synthesis of major neutrophil chemoattractants: leukotrienes. On the other hand, many THαβ related effector molecules are down-regulated such as killer cell immunoglobin-like receptors and natural cytotoxicity triggering receptors. (Table11)Immunoglobulin heavy constant alpha 1, delta, and gamma 1 are all suppressed during Alzheimer's disease. IGHA1 and IGHD are related to the regulatory B cell and immune-tolerance. IGHG1's gamma 1 immunoglobin is mainly the THαβ effector immunoglobin.

Chemokines and chemokine receptors are important mediators in recruiting T helper cells with different immunological pathways. (Table 12) Many chemokines and chemokine receptors are differentially regulated after Alzheimer's disease. CCR10 is down-regulated and its function is mucosal immunity for homing T cells to gut epithelium. CCR4 is down-regulated that is important chemokine receptor recruiting TH1 T helper cells. Down-regulated CX3CL1 is a chemokine ligand that recruit TH1 or TH9 effector cells such as T cells, NK cells, and monocytes(macrophages). Down-regulated CXCR3 is the chemokine receptor responding for recruiting activated TH1 cells. CXCR5 is also down-regulated which is related to B1 cell to produce natural antibody. CCR2 is activated and its function is to recruit T cells and monocytes (dendritic cells). CXCL1 is up-regulated and its function is to recruit neutrophils, main effectors of TH17 immunity. CXCR4 is also up-regulated and its function is related to myelopoiesis and homing neutrophils to bone marrow that is important in TH17 imminity. Those evidences also suggest that TH17 pathway is activated in Alzheimer's disease.

TNFα and Apoptosis related molecules are up-regulated after Alzheimer's disease

We found that majority of TNFα signaling molecules are up-regulated in Alzheimer's disease. (Table 13) TNFα is the key mediator in TH17 immunity, and it is important to mediate Wallerian degeneration. TNFα can activate downstream apoptotic signals such as caspase8. It is interesting to know that many apoptosis related genes are activated in Alzheimer's disease. These genes include FAS(TNF receptor member6), caspase1(IL1 beta convertase), caspase4, and caspase8. (Table 14) It is interesting to note that TNFα can trigger cellular apoptosis process during neuro-degeneration via activating these FAS and caspase machinery, especially caspase 8. Our microarray analysis can fully elucidate the pathophysiology of Alzheimer's disease.

Discussion

Until now, the pathogenesis of Alzheimer's disease is still unknown. Many theories are proposed for Alzheimer's disorder. Here, I am using logical principles and experimental observations to propose a complete model of Alzheimer's disease pathogenesis. In oldest theory, acetylcholine reduction is thought to be the pathophysiology of Alzheimer's disease. However, acetylcholine and other neurotransmitters reduction can be just due to neuron loss in Alzheimer's disorder. It is the effect, not the cause. The first hypothesis of Alzheimer's disease is Tau hypothesis. Taulopathy with hyperphosphorylated Tau tangles is found in Alzheimer's disease brain tissues. However, taulopathy is not specific to Alzheimer's disease. Taulopathy can also be found in many neuron diseases such as Pick's disease, multiple system atrophy, amyotrophic lateral sclerosis, frontotemporal dementia, and certain prion diseases. Thus, this disobeys the specific principle of the cause-effect relationship. That is to say each disease should have a specific cause. However, there is a fetal defect in the Tau hypothesis. Taulopathy with hyperphosphorylated Tau tangles can also be found in brain tissue of many people without Alzheimer's disease or other neurodegenerative diseases. That disobeys a basic logical principle (p->q is equal to –q->-p). If tau (p) causes Alzheimer's disease (q), then non-Alzheimer's disease (-q) must be associated with non-Taulopathy (-p). In those autopsy findings, that is not the case. In the other hand, amyloid beta accumulation can induce hyperphosphorylated tau. The physiological function of Tau is related to the microtubule transport system in axon. Thus, cellular mediating mechanism may be activated to affect the tau-microtubule transport system to reduce the transport of accumulated misfolded beta amyloid in neuron. In a PNAS paper, hyperphosphorylated tau can breakdown microtubule transport system(Alonso, Zaidi

et al. 1994). Thus, taulopathy is a common secondary change in many neurodegenerative disorders. However, tau abnormally is not the cause of these neurodegenerative diseases. The second popular hypothesis is amyloid hypothesis. Accumulation of misfolded beta amyloid protein is found in Alzheimer's disease brain tissue. This finding is specific to Alzheimer's disorder. Transgenic animal with mutant beta amyloid protein can successfully induce Alzheimer's disease in mice. Thus, beta amyloid hypothesis is likely to be the right cause. However, the amyloid alone hypothesis is still not the right one. Amyloid-immune hypothesis is actually the correct one. In a clinical trial published in Lancet, a vaccine against amyloid beta can still cause Alzheimer's disorder in old aged adults just like the control group(Holmes, Boche et al. 2008). This vaccine can completely clean out extracellular amyloid beta accumulation. Why can't this vaccine prevent Alzheimer's disease? The key reason is this vaccine induces autoimmune disorder which is the actual and direct reason of Alzheimer's disease. We can use the logical principle of p->q->r to see the relations. Amyloid beta accumulation (p) cause autoimmune reaction (q) against neuron, and then the autoimmune reaction (q) destroys neurons and causes Alzheimer's disorder (r). If we completely remove the causal factor p but we induce the direct causal factor q, we can still get the result r (Alzheimer's disease). That is why vaccine against beta amyloid will never work because it triggers autoimmune response.

Then, we will describe more clearly about the pathogenesis of Alzheimer's disease. TH17 autoimmune response plays an important role. Amyloid precursor protein (APP) of beta amyloid is a normal neuron membrane protein. Due to aging or gene mutation, the misfolded beta amyloid starts to accumulate in the neurons. It can also be released out extracellularly. There is a key factor to initiate host immune response: the heat shock proteins. Heat shock proteins are served as danger signals in host immunity against pathogens. Pathogens such as bacteria can induce fever; in turns, fever up-regulates these heat shock proteins. These heat shock proteins (HSP60 or HSP70) can bind to toll-like receptor 4(HSP60) or toll-like receptor 2(HSP70) to trigger host immunity.(Davies, Bacelar et al. 2006) Toll-like receptor 4 normally reacts to bacteria antigen such as LPS to trigger TH17 immunity. Toll-like receptor 2 usually reacts to bacteria antigen such as lipoteichoic acid to activate TH17 immunity. These activated TLRs can induce cytokines, chemokines, and costimulatory molecules to activate a certain immunological pathway. However, fever is not the solely cause to induce heat shock proteins. Accumulation of misfolded proteins can also induce heat shock proteins since heat shock proteins' basic functions are molecular chaperons. These heat shock proteins can be released out extracellularly to act on nearby immune cells such as microglia. Why is TH17 immunity induced specifically? In THαβ

immunity, virus replication induced dsRNA will activate TLR3 to trigger anti-virus immunity. In traditional TH1 immunity, intracellular bacteria will release unmethylated CpG DNA after digested by lysosomes to activate TLR9 to trigger ant-intrabacteria immunity. In the neurodegenerative disorders, only TLR4 or TLR2 is activated by heat shock proteins to induce IL-6 secretion and specific TH17 autoimmunity will be activated against misfolded beta amyloid. According to this microarray analysis, a lot of TH17 immunity related genes are up-regulated in Alzheimer's disease patients. Thus, TH17 autoimmunity is highly related to Alzheimer's disorder. In a study published in Immunity, TH17 helper cells can directly kill neuron cells after contact.(Egen and Ouyang 2010) In addition, TNFα, IL-6, and IL-1, key mediators of TH17 immunity, can cause Wallerian degeneration which is the major mechanism of most nerve degenerations.(Reichert, Levitzky et al. 1996; Raff, Whitmore et al. 2002) Transgenic mice with TNFα or IL-6 overexpression in brain can cause chronic neurodegeneration. These TH17 cells can recognize antigen (APP) in neuron membrane via auto antibody or TCR chain, and many cytokines will be released to kill the neurons. In addition, amyloid has also chemoattractant ability to attract immune cells. In some studies, amyloid beta is grouped as a kind of acute response protein which can be induced by IL-6. Thus, up-regulated IL-6 can up-regulate more amyloid beta to cause a vicious cycle. IL-1 and IL-6 can also up-regulate heat shock proteins to further increase immune danger signals.(Welsh, Welsh et al. 1991; Stephanou, Amin et al. 1997) This further exaggerates immune damage of neurons.

Epidemiology studies and experimental observations can point out the vital role of immune reaction in Alzheimer's disease. Many epidemiology researches observed that NSAID intake including aspirin can reduce the risk and severity of Alzheimer's disease.(in t' Veld, Ruitenberg et al. 2001) NSAIDs are drugs which have strong anti-inflammatory action. They can strongly inhibit a key immune regulator-NFkB and inhibit COX enzyme to prevent the synthesis of leukotrienes and prostaglandins. Apo E4 allele is found to increase the risk of Alzheimer's disease.(Blennow, de Leon et al. 2006) The physiological function of Apo E gene is related to anti-inflammatory reaction.(Ali, Middleton et al. 2005) It is worth noting that ApoE3 allele can bind to amyloid precursor protein to suppress its pro-inflammatory ability. Apo E4 allele is a dysfunctional allele which impairs in the normal anti-inflammatory regulation function. Thus, Apo E4 allele is related to the incidence of Alzheimer's disease. Aluminum is found to be related to Alzheimer's disease risk.(Levallois 1997) Aluminum is related to an immune adjuvant and it can deposit in brain to trigger immune reaction. Thus, it is also possible that immune reaction induced by

Aluminum triggers Alzheimer's disease. Estrogen is found to have some protective role from Alzheimer's disorder. Estrogen can play important role of immune-regulation, especially in pregnant women to prevent immune reaction against fetus. Estrogen can expand Treg expansion in a previous study.(Polanczyk, Carson et al. 2004) Women are easier to get many autoimmune diseases compared to men. The reason can be due to skewed X chromosome inactivation (not 50:50 balance) confirmed in scleroderma and autoimmune thyroditis.(Puck and Willard 1998) Estrogen is actually anti-inflammatory. Down syndrome patients who have trisomy 21 increase risk of Alzheimer's disorder can be due to the excessive copy of Amyloid beta protein (APP)(Moncaster, Pineda et al. 2010). Familial Alzheimer's disease is associated with a point mutation of APP gene or Presenilin genes which interact with ϒ secretase to produce amyloid beta fragment from APP. Another important type of dementia is vascular dementia which is due to the atherosclerosis-stroke. Atherosclerosis is basically an auto-immune inflammation against blood vessels with elevated cytokines, CRP, monocytes, and lymphocytes. Systemic infection and inflammation can cause a long-term decline of cognitive state in Alzheimer's disease patients. A study showed that autoantibody against amyloid beta is increased in elderly and is related to Alzheimer's disease. Increased T cell reactivity to amyloid beta is also found in elderly patients with Alzheimer's disorder. IL-1, IL-6, and TNFα polymorphisms are related to the risk of Alzheimer's disease. These above cytokines are important TH17 cytokines. These epidemiology findings support that immune reaction plays an important role in Alzheimer's disease. In animal studies, transgenic mice with overexpressed or mutant amyloid beta can induce Alzheimer's disease. Several researchers also found that LPS injection in mice can also produce Alzheimer's disorder in mice. LPS can trigger strong TH17 immunity. Thus, TH17 immunity triggered in these mice may react against autoantigen of brain tissue to cause Alzheimer's disease. In Alzheimer's disease, there is no CD8 T cell infiltration found usually in encephalitis. Thus, the neurodegenerative reaction in Alzheimer's disorder is more likely due to indirect response by cytokines such as TNFα and IL-1. Another important TH17 or Treg cytokine-TGFβ is also related to the pathogenesis of Alzheimer's disease. It can either promote or suppress the disease by initiating TH17 or Treg pathway. In addition, overactivity of microglias to secrete TH17 cytokines including IL-1, TNFα, and IL-6 is also noted in Alzheimer's disease, especially when they are stimulated by amyloid beta. Complement system as well as peroxide is also up-regulated in Alzheimer's disorder and that system is associated to TH17 anti-bacterial immunity. Heat shock proteins up-regulations are found in many neurodegenerative disorders(Urbanics 2002). A study showed that HSP60 can cause CNS neurodegeneration in wild-type mice but not in TLR4 knock-out mice.(Lehnardt,

Schott et al. 2008) It points out that heat shock proteins and toll-like receptors play important roles in neurodegenerative disorders.

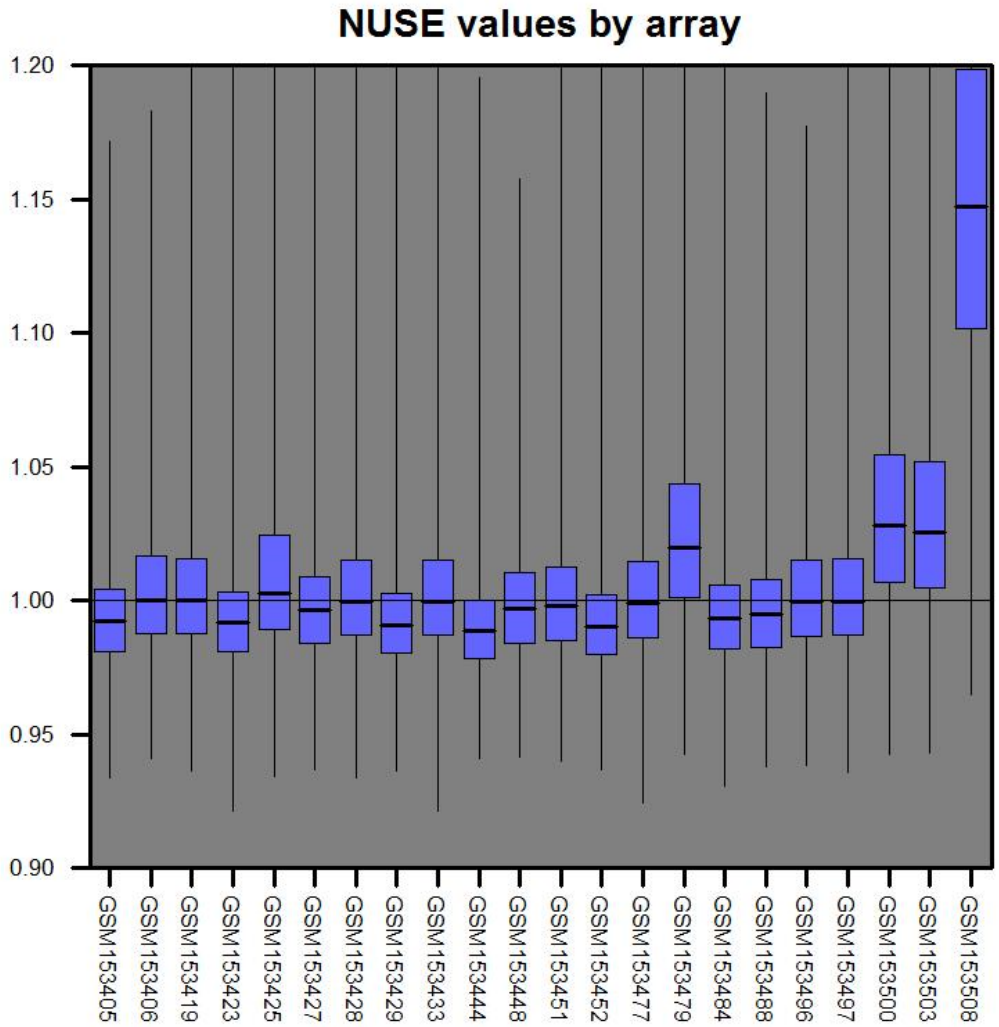
Witebsky's postulates are the standard criteria to decide if a disorder is an autoimmune disease. There are three requirements in Witebsky's postulates: 1. Direct evidence from transfer of pathogenic antibody or T cells 2. Indirect evidence based on reproduction of the autoimmune disease in experimental animal 3. Circumstantial evidence from clinical clues. We can check if Alzheimer's disease fulfills the above criteria. First of all, pathogenic autoreactive T cells and autoantibody against beta amyloid have been observed in Alzheimer's disease patients. However, direct human-to-human T cells or antibodies transfer is not feasible clinically. However, autoantibody from human serum in Alzheimer's disease patients can cause typical brain lesion in animals. CD45RO+ T cells (memory T cells) infiltration is found in Alzheimer patients' brains. It suggests to match the first criteria. Second, beta amyloid injection or transgene can induce autoantibody as as well as Alzheimer's disease in mice. This suggests the second criteria is met. Third, vaccine against beta amyloid cannot successfully prevent Alzheimer's disease. Autoimmunity with encephalitis as well as Alzheimer's disease was induced in the vaccine recipients. In addition, TH17 overactivity was found in Alzheimer's disease patients. In a Lancet paper, risk of Alzheimer's disease decreases in Rheumatoid arthritis patients treated with immunosuppressant agents. Immunosuppressant IVIG or NSAID can suppress Alzheimer's disease progression. HLA-A2, HLA-B7, and HLA-BRB1*03 are associated with the incidence of Alzheimer's disease. Type 1 diabetes and autoimmune thyroiditis also increase the risk of Alzheimer's disease. Those all suggest that the third criteria is met. In summary, TH17 autoimmunity against amyloid beta is the cause of Alzheimer's disease. Vaccines against amyloid beta can cause severe brain inflammation such as encephalitis or brain edema. It suggests that amyloid beta vaccine could cause TH1, TH9 (THαβ), or TH17 autoimmunity. This vaccine cannot prevent Alzheimer's disease but trigger Alzheimer's disease. The actually correct strategy is to induce immune tolerance to amyloid beta. When we know the pathogenesis of Alzheimer's disorder, we can design ideal method to deal with this common detrimental neurodegenerative disease.

Figure legends

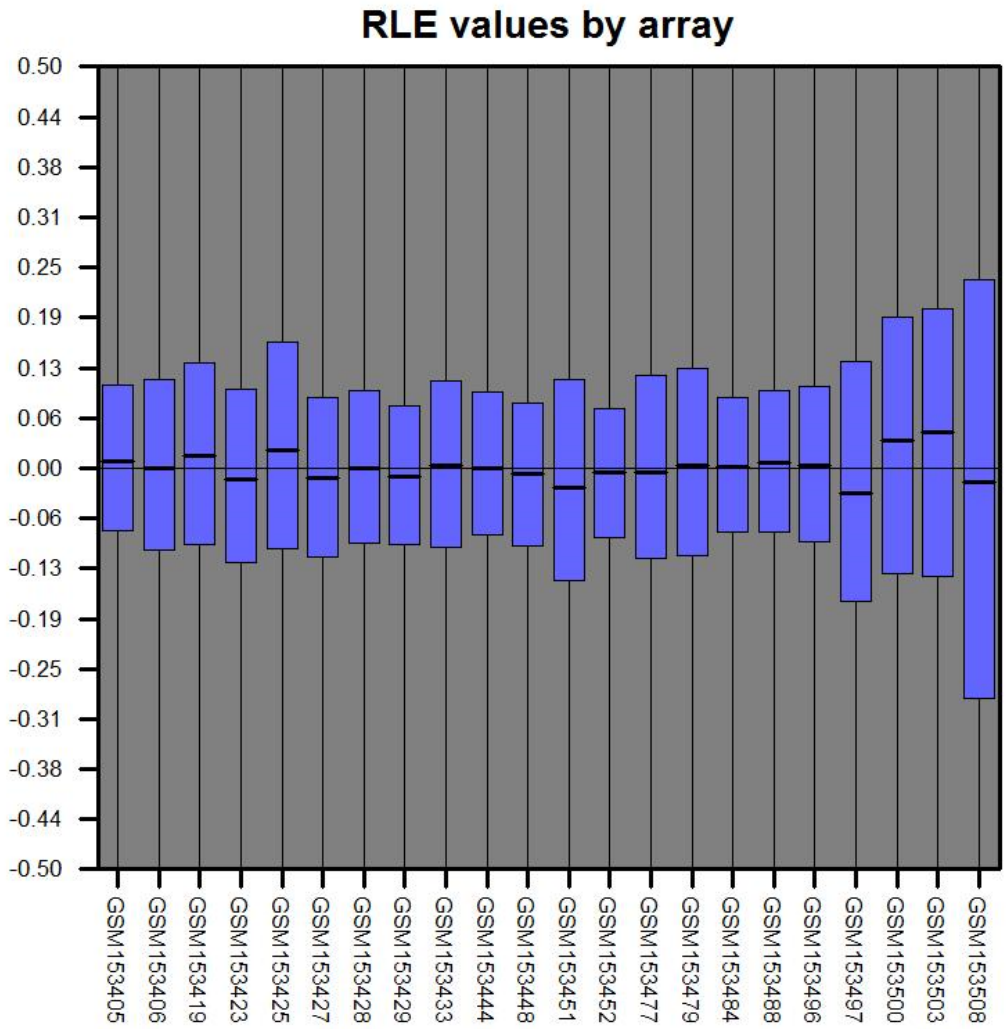
Figure 1. RMA express plot for selecting samples in normal healthy controls.
1-A NUSE boxplot for normal control
1-B RLE boxplot for normal control
1-C RLE-NUSE multiplot for normal control
1-D RLE-NUSE T2 plot for normal control

Figure 2. RMA express plot for selecting samples in Alzheimer's disease patients.
2-A NUSE boxplot for Alzheimer's disease patients
2-B RLE boxplot for Alzheimer's disease patients
2-C RLE-NUSE multiplot for Alzheimer's disease patients
2-D RLE-NUSE T2 plot for Alzheimer's disease patients

Figure 1



1-A



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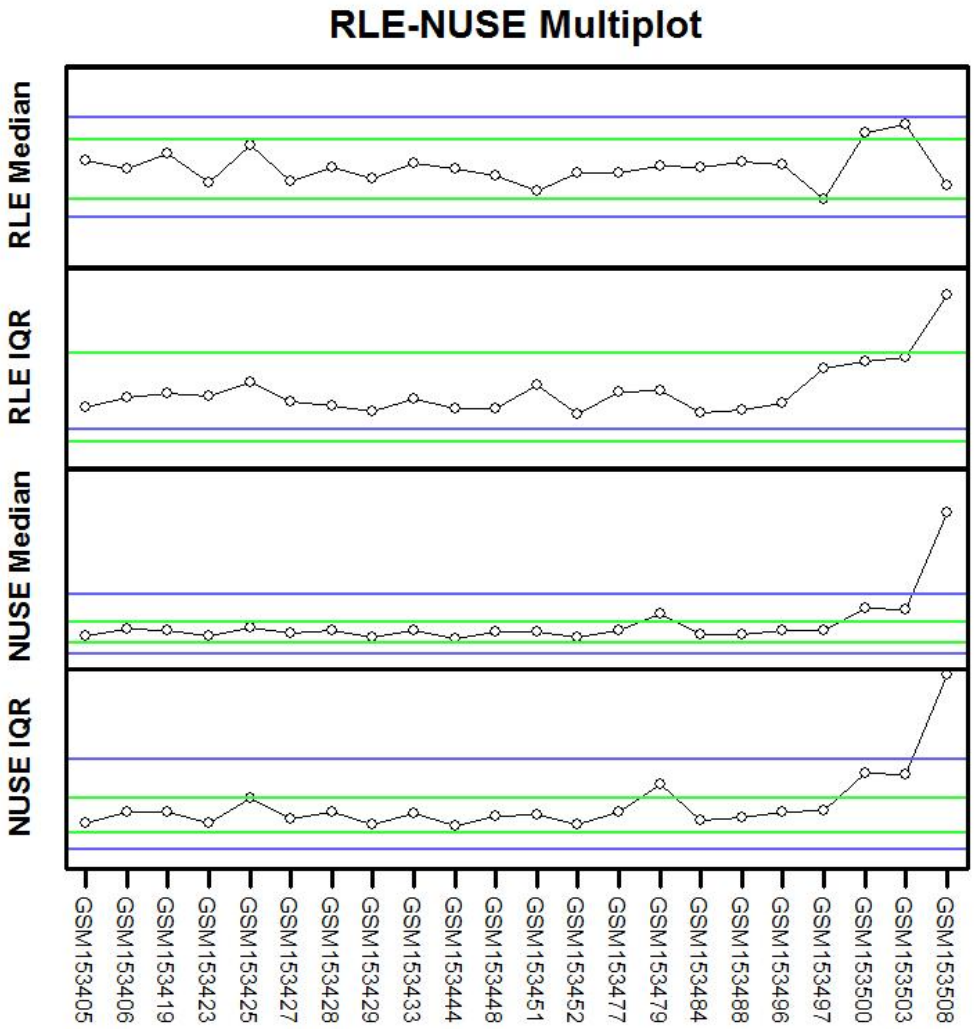
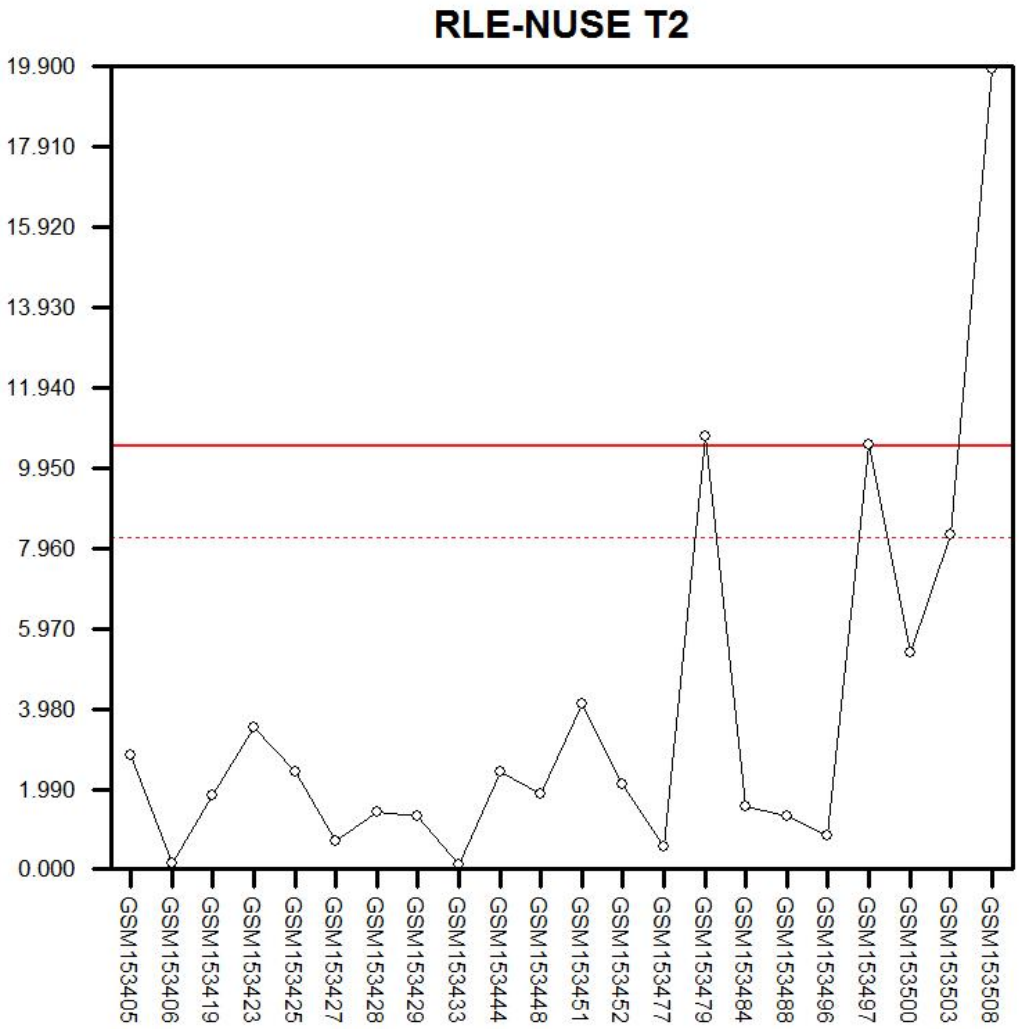
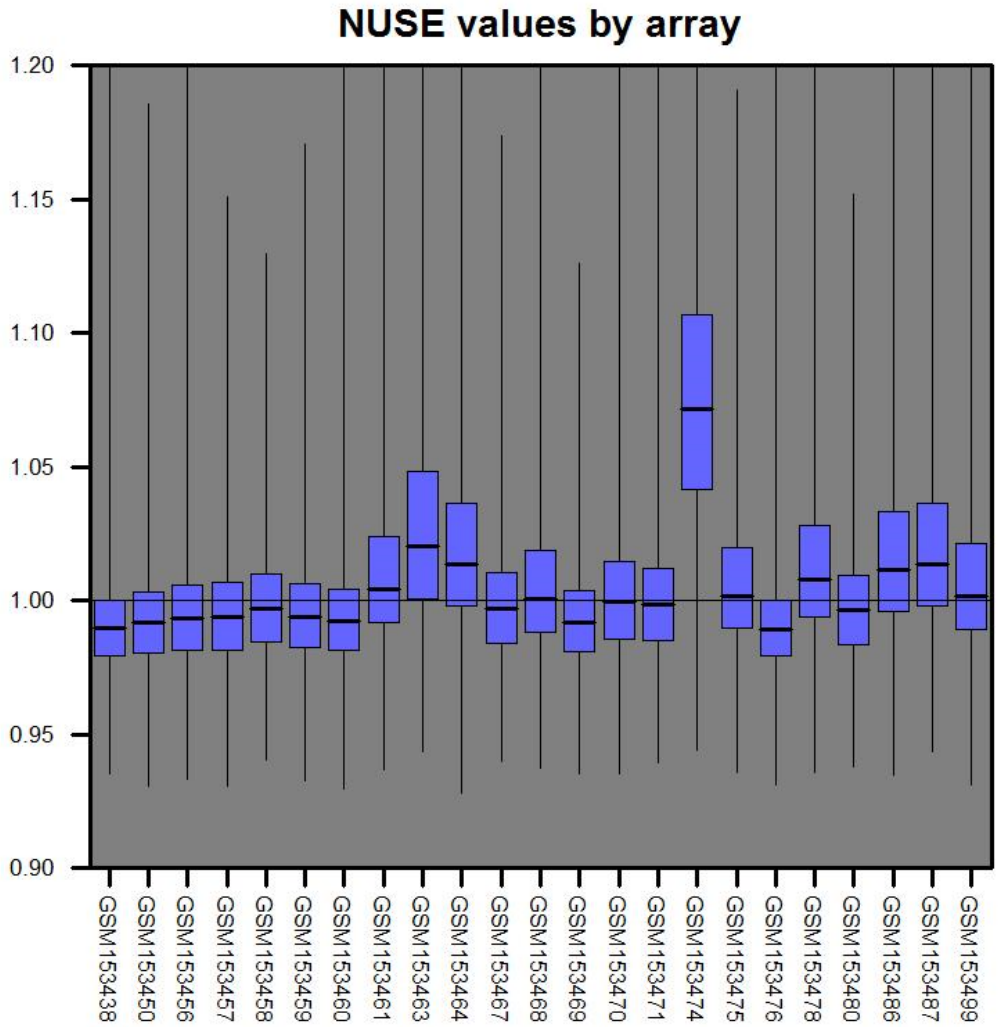


1-C



1-D

Figure 2



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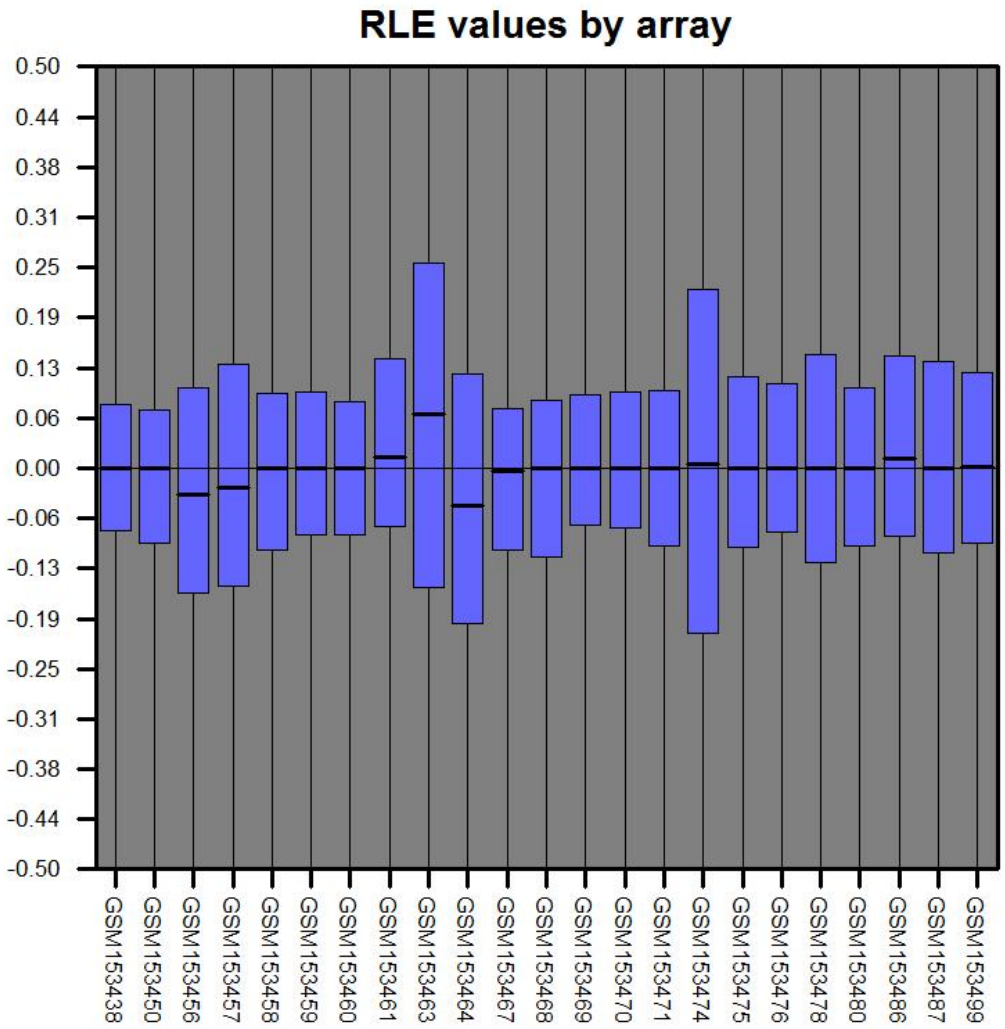
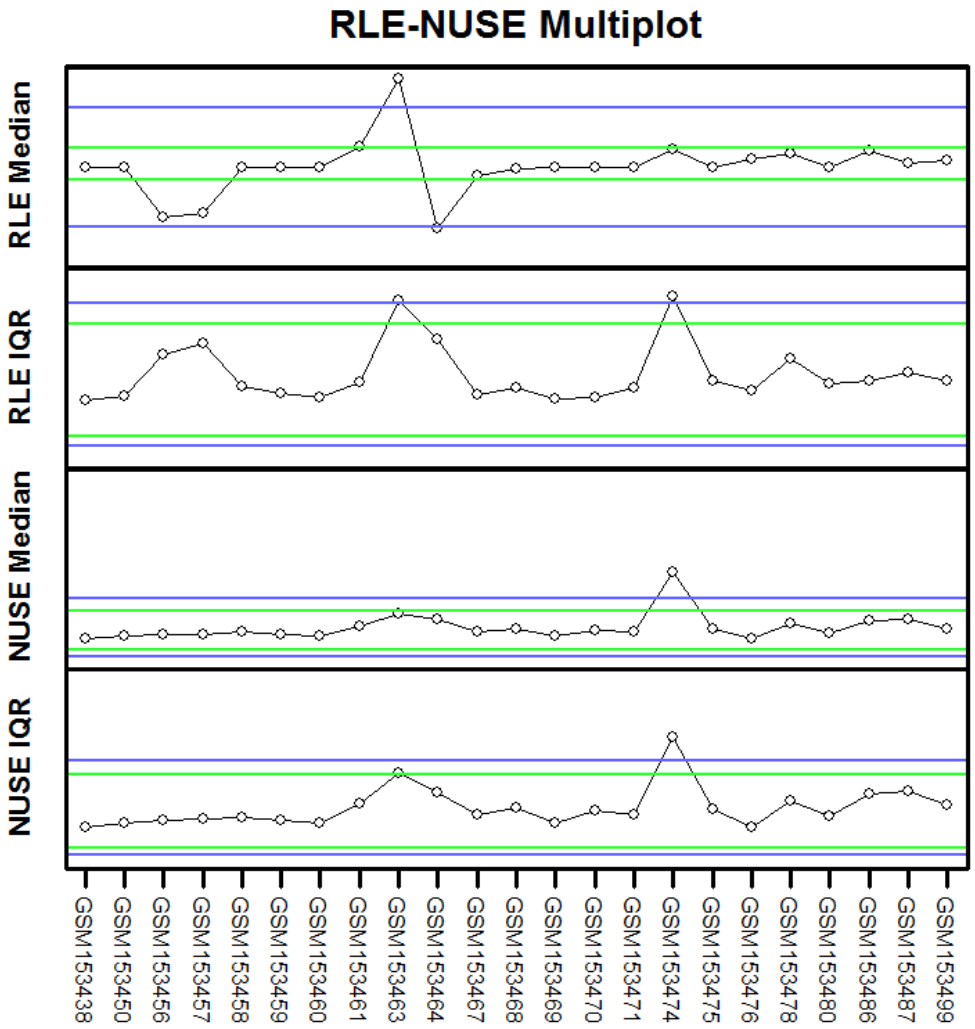


2-B



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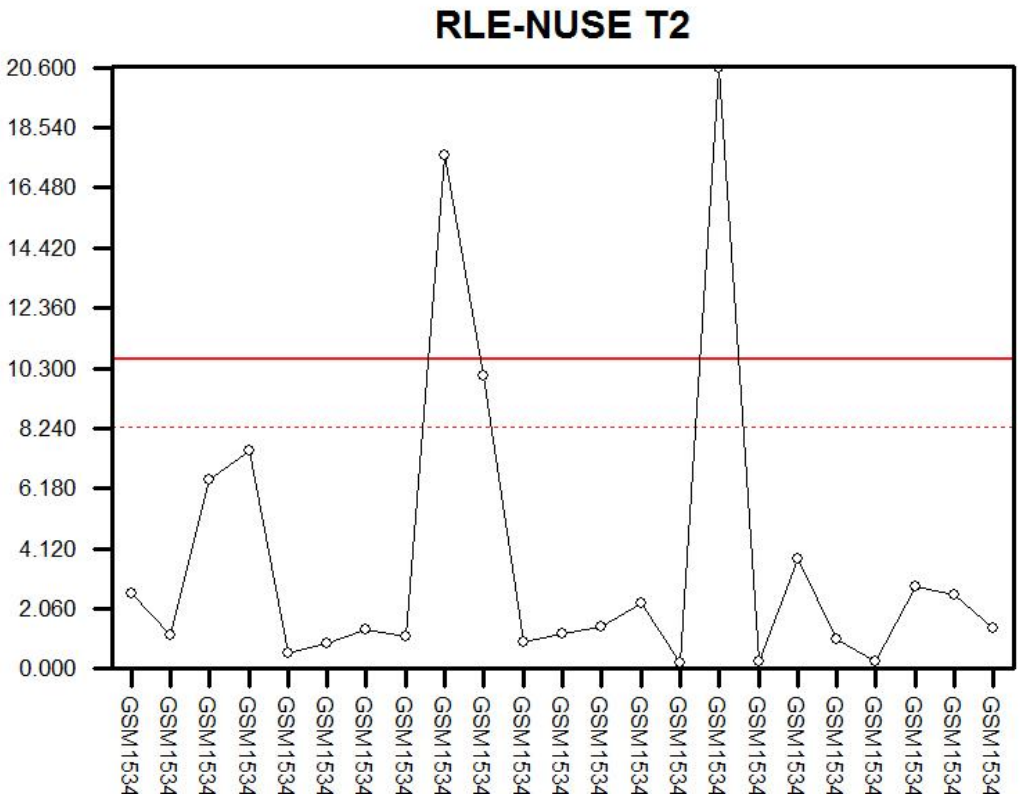

2-D

Table 1. Heat shock protein up-regulation in Alzheimer's disease

HSP

Probeset	Foldchange	Direction	P value	Gene	Description
200880_at	1.1264739	up	0.041538	DNAJA1	DnaJ (Hsp40) homolog,A1
200881_s_at	1.1773959	up	0.042676	DNAJA1	DnaJ (Hsp40) homolog, A1
209157_at	1.1217633	up	0.01595	DNAJA2	DnaJ (Hsp40) homolog, A2
214338_at	1.1134291	down	0.02154	DNAJB12	DnaJ (Hsp40) homolog B12
219237_s_at	1.2513392	up	0.036463	DNAJB14	DnaJ (Hsp40) homolog B14
212817_at	1.1041778	down	0.019418	DNAJB5	DnaJ (Hsp40) homolog, B5
209015_s_at	1.2039303	up	0.00671	DNAJB6	DnaJ (Hsp40) homolog, B6
208810_at	1.1866026	up	0.003965	DNAJB6	DnaJ (Hsp40) homolog, B6
208811_s_at	1.1367813	up	0.002279	DNAJB6	DnaJ (Hsp40) homolog, B6
213919_at	1.1187105	down	0.019447	DNAJC4	DnaJ (Hsp40) homolog, C4
213092_x_at	1.1066989	up	0.031719	DNAJC9	DnaJ (Hsp40) homolog, C 9
205824_at	1.1317875	down	0.040135	HSPB2	heat shock 27kDa protein 2
200807_s_at	1.1752084	up	0.030451	HSPD1/A1A	heat shock 60kDa protein 1
200800_s_at	1.2298127	up	0.041047	HSPA1B	heat shock 70kDa protein 1A/1B
117_at	1.2525237	up	5.16E-05	HSPA6	heat shock 70kDa protein 6
213418_at	1.3766227	up	1.73E-05	HSPA6	heat shock 70kDa protein 6
200942_s_at	1.1727859	up	0.005981	HSBP1	heat shock factor binding protein 1
210211_s_at	1.304165	up	0.015253	HSP90AA1	heat shock protein 90kDa alpha 1
211968_s_at	1.3834474	up	0.009443	HSP90AA1	heat shock protein 90kDa alpha 1
214328_s_at	1.3160697	up	0.006936	HSP90AA1	heat shock protein 90kDa alpha 1
219284_at	1.1855927	up	0.017403	HSPBAP1	HSPB (heat shock 27kDa) protein 1

Table 2. Cyclophilin up-regulation in Alzheimer's disease

Cyclophilin

Probeset	FoldChange	Direction	P value	Gene	Description
201293_x_at	1.1661414	up	0.033451	PPIA	peptidylprolyl isomerase A (cyclophilin A)
211765_x_at	1.1487285	up	0.041849	PPIA	peptidylprolyl isomerase A (cyclophilin A)
211978_x_at	1.1397567	up	0.042275	PPIA	peptidylprolyl isomerase A (cyclophilin A)
212661_x_at	1.1690186	up	0.028594	PPIA	peptidylprolyl isomerase A (cyclophilin A)
213483_at	1.2117164	up	6.38E-04	PPWD1	peptidylprolyl isomerase domain and WD 1
201489_at	1.1635383	up	0.001215	PPIF	peptidylprolyl isomerase F
201490_s_at	1.1665412	up	0.013164	PPIF	peptidylprolyl isomerase F
208993_s_at	1.2084992	up	0.012148	PPIG	peptidylprolyl isomerase G (cyclophilin G)

Table 3. FK506 bind protein down-regulation in Alzheimer's disease

FK506BP

ProbeSet	FoldChange	Direction	P value	Gene	Description
215381_at	1.1499108	down	0.005959	FRAP1	FK506 binding protein 12-1
200709_at	1.1636457	up	0.009177	FKBP1A	FK506 binding protein 1A
206857_s_at	1.1553942	down	0.048362	FKBP1B	FK506 binding protein 1B
203391_at	1.101353	down	0.005849	FKBP2	FK506 binding protein 2
40850_at	1.1701775	down	0.006909	FKBP8	FK506 binding protein 8

Table 4. Toll-like receptor up-regulation in Alzheimer's disease

TLR

ProbeSet	FoldChange	Direction	P value	Gene	Description
210176_at	1.3017664	up	0.005571	TLR1	toll-like receptor 1
204924_at	1.211758	up	0.032576	TLR2	toll-like receptor 2
220832_at	1.2938874	up	0.001242	TLR8	toll-like receptor 8

Table 5. Proteasome up-regulation in Alzheimer's disease

Proteasome-related genes

ProbeSet	FoldChange	Direction	P value	Gene	Description
201699_at	1.2815031	up	0.01945	PSMC6	proteasome ATPase, 6
200882_s_at	1.1032741	up	0.04081	PSMD4	proteasome non-ATPase, 4
210459_at	1.1209667	down	0.01026	PSMD4	proteasome non-ATPase, 4
211609_x_at	1.1008434	up	0.02654	PSMD4	proteasome non-ATPase, 4
202753_at	1.1955253	up	0.00931	PSMD6	proteasome non-ATPase, 6
212222_at	1.1030655	up	0.02647	PSME4	proteasome activator subunit 4
201052_s_at	1.280426	down	0.0179	PSMF1	proteasome inhibitor subunit 1
201053_s_at	1.1621141	down	0.04628	PSMF1	proteasome inhibitor subunit 1
201676_x_at	1.1624885	up	0.00582	PSMA1	proteasome subunit, alpha 1
211746_x_at	1.1451734	up	0.0129	PSMA1	proteasome subunit, alpha 1
201114_x_at	1.1327786	up	0.04265	PSMA7	proteasome subunit, alpha 7
216088_s_at	1.1582605	up	0.0484	PSMA7	proteasome subunit, alpha 7
201400_at	1.2038707	up	0.00801	PSMB3	proteasome subunit, beta 3
202244_at	1.1788965	up	0.0491	PSMB4	proteasome subunit, beta 4
209040_s_at	1.1320962	up	0.03885	PSMB8	proteasome subunit, beta 8

Table 6. Ubiquitin up-regulation in Alzheimer's disease

ProbeSet	FoldChange	Direction	P value	Gene	Description
208909_at	1.13722	up	0.01682	UQCRFS1	ubiquinol-cytochrome c reductase 1
220746_s_at	1.1156392	up	0.02947	UIMC1	ubiquitin interaction motif containing 1
212756_s_at	1.1666127	up	0.00571	UBR2	ubiquitin protein ligase E3 c 2
212760_at	1.1963028	up	0.00307	UBR2	ubiquitin protein ligase E3 c 2
208882_s_at	1.1337341	up	0.00926	UBR5	ubiquitin protein ligase E3 c 5
208883_at	1.2222811	up	1.54E-04	UBR5	ubiquitin protein ligase E3 c 5
208884_s_at	1.1282661	up	0.01432	UBR5	ubiquitin protein ligase E3 c 5
212278_x_at	1.1635853	down	0.00729	UBE3A	ubiquitin protein ligase E3A
212404_s_at	1.1012999	down	0.03714	UBE3B	ubiquitin protein ligase E3B
202412_s_at	1.1894782	up	0.02288	USP1	ubiquitin specific peptidase 1
209475_at	1.1614392	up	0.03502	USP15	ubiquitin specific peptidase 15
210681_s_at	1.2581427	up	4.46E-04	USP15	ubiquitin specific peptidase 15
220419_s_at	1.16619	up	0.00656	USP25	ubiquitin specific peptidase 25
221654_s_at	1.2221688	up	0.00219	USP3	ubiquitin specific peptidase 3
212513_s_at	1.334952	up	0.00414	USP33	ubiquitin specific peptidase 33
212066_s_at	1.1013068	up	0.04657	USP34	ubiquitin specific peptidase 34
211800_s_at	1.35255	up	0.0053	USP4	ubiquitin specific peptidase 4
221518_s_at	1.2312088	up	0.00973	USP47	ubiquitin specific peptidase 47
220079_s_at	1.2241454	up	1.05E-04	USP48	ubiquitin specific peptidase 48
202745_at	1.1060245	up	0.03067	USP8	ubiquitin specific peptidase 8
201099_at	1.174015	up	0.01164	USP9X	ubiquitin specific peptidase 9, X
202038_at	1.1676221	up	0.01504	UBE4A	ubiquitination factor E4A
217823_s_at	1.3819482	up	0.00296	UBE2J1	ubiquitin-conjugating enzyme E2, J1
217824_at	1.2016946	up	9.66E-04	UBE2J1	ubiquitin-conjugating enzyme E2, J1
217826_s_at	1.3065044	up	0.00633	UBE2J1	ubiquitin-conjugating enzyme E2, J1
202333_s_at	1.300187	up	7.47E-04	UBE2B	ubiquitin-conjugating enzyme E2B
211763_s_at	1.1667289	up	0.01652	UBE2B	ubiquitin-conjugating enzyme E2B
214590_s_at	1.1247846	up	0.01648	UBE2D1	ubiquitin-conjugating enzyme E2D 1
201343_at	1.148696	up	0.04701	UBE2D2	ubiquitin-conjugating enzyme E2D 2
200667_at	1.3642609	up	3.52E-05	UBE2D3	ubiquitin-conjugating enzyme E2D 3
200668_s_at	1.1327549	up	0.04681	UBE2D3	ubiquitin-conjugating enzyme E2D 3
200669_s_at	1.165956	up	0.00506	UBE2D3	ubiquitin-conjugating enzyme E2D 3
209141_at	1.1685846	up	0.00399	UBE2G1	ubiquitin-conjugating enzyme E2G 1
202347_s_at	1.1953372	up	0.00179	UBE2K	ubiquitin-conjugating enzyme E2K
217978_s_at	1.1428812	up	0.01252	UBE2Q1	ubiquitin-conjugating enzyme E2Q 1
209115_at	1.3230728	up	0.0043	UBA3	ubiquitin-like modifier activating enzyme 3

Table 7. MHC gene up-regulation in Alzheimer's disease

MHC

ProbeSet	FoldChange	Direction	P value	Gene	Description
217436_x_at	1.1952208	up	3.12E-04	HLA-A //	major histocompatibility complex, class I, A/B/G/H/J
208729_x_at	1.2380992	up	0.002392	HLA-B	major histocompatibility complex, class I, B
209140_x_at	1.1349622	up	0.029995	HLA-B	major histocompatibility complex, class I, B
211911_x_at	1.2645333	up	0.00133	HLA-B	major histocompatibility complex, class I, B
211799_x_at	1.225191	up	0.011861	HLA-C	major histocompatibility complex, class I, C
214459_x_at	1.1161561	up	0.040349	HLA-C	major histocompatibility complex, class I, C
200904_at	1.1801262	up	0.032202	HLA-E	major histocompatibility complex, class I, E
204806_x_at	1.179907	up	0.003565	HLA-F	major histocompatibility complex, class I, F
221875_x_at	1.1951036	up	0.001641	HLA-F	major histocompatibility complex, class I, F
221978_at	1.1210384	up	0.04485	HLA-F	major histocompatibility complex, class I, F
210514_x_at	1.1745148	up	0.00645	HLA-G	major histocompatibility complex, class I, G
211528_x_at	1.1169857	up	0.031831	HLA-G	major histocompatibility complex, class I, G
211529_x_at	1.1736183	up	0.003765	HLA-G	major histocompatibility complex, class I, G
211142_x_at	1.1199778	down	6.93E-04	HLA-DOA	major histocompatibility complex, class II, DO a
215536_at	1.112155	down	0.007695	HLA-DQB2	major histocompatibility complex, class II, DQ b2
208894_at	1.1855354	up	0.035907	HLA-DRA	major histocompatibility complex, class II, DR a
210982_s_at	1.1979958	up	0.024158	HLA-DRA	major histocompatibility complex, class II, DR a
209312_x_at	1.1849538	up	0.025	HLA-DRB1/4/5	major histocompatibility complex, class II, DRb1/4/5

Table 8. General immune-related gene expression in Alzheimer's disease

ProbeSet	FoldChange	Direction	P value	Gene	Description
General Immune-related genes					
201328_at	1.15958	up	0.029563	ETS2	v-ets erythroblastosis virus E26 oncogene homolog 2
209189_at	1.2658114	up	0.002918	FOS	v-fos FBJ murine osteosarcoma viral oncogene
207616_s_at	1.2377095	up	5.69E-04	TANK	TRAF family member-associated NFKB activator
209451_at	1.124753	up	0.036047	TANK	TRAF family member-associated NFKB activator
203574_at	1.2275279	up	0.017317	NFIL3	nuclear factor, interleukin 3 regulated
207857_at	1.214883	up	0.01645	LILRA2	leukocyte immunoglobulin-like receptor, A2
211100_x_at	1.184132	up	0.009633	LILRA2	leukocyte immunoglobulin-like receptor, A2
211101_x_at	1.1984037	up	0.003557	LILRA2	leukocyte immunoglobulin-like receptor, A2
208594_x_at	1.1009715	up	0.026265	LILRA6	leukocyte immunoglobulin-like receptor,A6
210784_x_at	1.1701205	up	0.014631	LILRA6/B3	leukocyte immunoglobulin-like receptor, A6/B3
207697_x_at	1.1894032	up	0.01184	LILRB2	leukocyte immunoglobulin-like receptor, subfamily B2
210146_x_at	1.1990024	up	0.037416	LILRB2	leukocyte immunoglobulin-like receptor, subfamily B2
207072_at	1.5166031	up	0.004379	IL18RAP	interleukin 18 receptor accessory protein
Immunosuppressant related genes					
203084_at	1.1017954	down	0.011346	TGFB1	transforming growth factor, beta 1
221333_at	1.1010736	down	0.044052	FOXP3	forkhead box P3
221334_s_at	1.1091903	down	0.001242	FOXP3	forkhead box P3
217073_x_at	1.1063635	down	0.024542	APOA1	apolipoprotein A-I
206894_at	1.1067672	down	0.01217	APOA4	apolipoprotein A-IV
205820_s_at	1.1096109	down	9.17E-04	APOC3	apolipoprotein C-III
Intergrin					
213416_at	1.2871763	up	0.031242	ITGA4	integrin, alpha 4
205055_at	1.1200194	up	0.008725	ITGAE	integrin, alpha E
210184_at	1.131516	up	0.009814	ITGAX	integrin, alpha X
211945_s_at	1.2406691	up	0.040016	ITGB1	integrin, beta 1
204990_s_at	1.1103201	down	0.01161	ITGB4	integrin, beta 4
211905_s_at	1.1428707	down	4.90E-05	ITGB4	integrin, beta 4
214292_at	1.1412681	down	0.006052	ITGB4	integrin, beta 4
204949_at	1.2761976	up	0.013495	ICAM3	intercellular adhesion molecule 3

Table 9. TH17 signal up-regulation after Alzheimer's disease

ProbeSet	FoldChange	Direction	P value	Gene	Description
TH17 signals					
205227_at	1.1329354	up	0.028928	IL1RAP	interleukin 1 receptor accessory protein
216245_at	1.108872	down	0.003656	IL1RN	interleukin 1 receptor antagonist
212195_at	1.4201341	up	0.023924	IL6ST	interleukin 6 signal transducer
202859_x_at	1.1853907	up	0.046275	IL8	interleukin 8
207008_at	1.2570976	up	0.024554	IL8RB	interleukin 8 receptor, beta
205159_at	1.2810134	up	0.010892	CSF2RB	colony stimulating factor 2 receptor, beta
205546_s_at	1.1300622	up	0.024324	TYK2	tyrosine kinase 2
205842_s_at	1.2038056	up	0.003723	JAK2	Janus kinase 2
212501_at	1.2887142	up	3.53E-04	CEBPB	CCAAT/enhancer binding protein beta
203973_s_at	1.3579507	up	8.63E-04	CEBPD	CCAAT/enhancer binding proteindelta
TH1, TH2, THαβ signals					
202727_s_at	1.3582387	up	2.06E-04	IFNGR1	interferon gamma receptor 1
211676_s_at	1.3067635	up	0.005434	IFNGR1	interferon gamma receptor 1
201642_at	1.27636	up	0.001005	IFNGR2	interferon gamma receptor 2
204912_at	1.2648444	up	0.008919	IL10RA	interleukin 10 receptor, alpha
217702_at	1.1927272	down	0.002406	IL27RA	interleukin 27 receptor, alpha
207844_at	1.135316	down	0.01711	IL13	interleukin 13
207952_at	1.1004333	down	0.004033	IL5	interleukin 5
201887_at	1.2225778	up	0.023643	IL13RA1	interleukin 13 receptor, alpha 1
201888_s_at	1.1367354	up	0.041201	IL13RA1	interleukin 13 receptor, alpha 1
203233_at	1.1382436	up	0.038157	IL4R	interleukin 4 receptor
208164_s_at	1.1225677	down	0.003385	IL9R/P3	interleukin 9 receptor/pseudogene 3
206553_at	1.1051463	down	0.013873	OAS2	2'-5'-oligoadenylate synthetase 2,
210797_s_at	1.1029738	down	0.016554	OASL	2'-5'-oligoadenylate synthetase-like
202411_at	1.1413709	down	0.041661	IFI27	interferon, alpha-inducible protein 27
Treg/Th17signaling					
203076_s_at	1.1117328	up	0.002414	SMAD2	SMAD family member 2
203077_s_at	1.1010205	up	0.01076	SMAD2	SMAD family member 2
202527_s_at	1.1321155	up	0.008181	SMAD4	SMAD family member 4
209887_at	1.1434844	down	0.006586	SMAD6	SMAD family member 6
213565_s_at	1.1360908	down	7.04E-04	SMAD6	SMAD family member 6
203084_at	1.1017954	down	0.011346	TGFB1	TGF, beta 1
208944_at	1.2490977	up	0.001123	TGFBR2	TGF, beta receptor II
221333_at	1.1010736	down	0.044052	FOXP3	forkhead box P3
221334_s_at	1.1091903	down	0.001242	FOXP3	forkhead box P3

Table 10. TH17 effector molecules in Alzheimer's disease

S100 binding proteins				
200660_at	1.286944 up	0.00474	S100A11	S100 calcium binding protein A11
208540_x_at	1.16087 up	0.018293	S100A11/P	S100 calcium binding protein A11 /// pseudogene
217728_at	1.256855 up	0.004132	S100A6	S100 calcium binding proteinA6
203535_at	1.257387 up	0.008377	S100A9	S100 calcium binding proteinA9
218370_s_at	1.219779 up	0.002595	S100PBP	S100P binding protein
Granulysin				
37145_at	1.470512 up	0.01636	GNLY	granulysin
205495_s_at	1.499066 up	0.012705	GNLY	granulysin
SERPINB				
212268_at	1.160325 up	0.025175	SERPINB1	serpin peptidase inhibitor, clade B member 1
213572_s_at	1.186531 up	0.048553	SERPINB1	serpin peptidase inhibitor, clade B member 1
Ferritin				
200748_s_at	1.174753 up	0.002752	FTH1	ferritin, heavy polypeptide 1
214211_at	1.247263 up	1.31E-04	FTH1	ferritin, heavy polypeptide 1
Fc receptor				
204232_at	1.18774 up	0.016998	FCER1G	Fc fragment of IgE, high affinity I, receptor gamma
210992_x_at	1.224164 up	0.005917	FCGR2C	Fc fragment of IgG, low affinity IIc, receptor(CD32)
211395_x_at	1.246557 up	0.005104	FCGR2C	Fc fragment of IgG, low affinity IIc, receptor(CD32)
218831_s_at	1.205921 up	0.002179	FCGRT	Fc fragment of IgG, receptor, transporter, alpha
C-type lectin				
206682_at	1.136811 up	0.019741	CLEC10A	C-type lectin domain family 10, member A
209732_at	1.160031 up	0.027833	CLEC2B	C-type lectin domain family 2, member B
220132_s_at	1.130485 up	0.005903	CLEC2D	C-type lectin domain family 2, member D
219947_at	1.221832 up	0.021994	CLEC4A	C-type lectin domain family 4, member A
221724_s_at	1.12417 up	0.033972	CLEC4A	C-type lectin domain family 4, member A
219859_at	1.197984 up	2.96E-04	CLEC4E	C-type lectin domain family 4, member E
221698_s_at	1.270019 up	0.009048	CLEC7A	C-type lectin domain family 7, member A
Cathepsin				
201487_at	1.241428 up	0.002623	CTSC	cathepsin C
202295_s_at	1.153163 up	0.038832	CTSH	cathepsin H
202902_s_at	1.207185 up	0.00985	CTSS	cathepsin S
210042_s_at	1.537711 up	0.001582	CTSZ	cathepsin Z
Lipoxygenase				
204446_s_at	1.193272 up	0.027604	ALOX5	arachidonate 5-lipoxygenase
214366_s_at	1.235728 up	0.006579	ALOX5	arachidonate 5-lipoxygenase
204174_at	1.164518 up	0.041447	ALOX5AP	arachidonate 5-lipoxygenase-activating

Table 11. Other immune-related genes in Alzheimer's disease

NK related receptors					
ProbeSet	Fold	Direct	P value	Gene	Description
Activating receptors					
217045_xat	1.1163526	down	0.0204	NCR2	natural cytotoxicity triggering receptor 2
217493_xat	1.111958	down	0.0111	NCR2	natural cytotoxicity triggering receptor 2
211688_xat	1.1727773	down	0.0138	KIR3DL2	killer cell immunoglobulin-like receptor,2
216907_xat	1.1327724	down	0.045	KIR3DL2	killer cell immunoglobulin-like receptor,2
217318_xat	1.1268805	down	0.0173	KIR2DL1	killer cell immunoglobulin-like receptor,1
211242_xat	1.1063491	down	0.0281	KIR2DL4	killer cell immunoglobulin-like receptor, 4
Inhibitory receptors					
206785_sat	1.1346893	up	0.0453	KLRC1/2	killer cell lectin-likereceptorsubfamilyC1/2
220646_sat	1.3712647	up	0.0435	KLRF1	killer cell lectin-like receptor subfamily F1
Immunoglobins					
217169_at	1.1120038	down	0.0489	IGHA1	immunoglobulin heavy constant alpha 1
213674_xat	1.1363686	down	0.009	IGHD	immunoglobulin heavy constant delta
211693_at	1.1722538	down	0.0036	IGHG1	Immunoglobulin heavy constant gamma1
215118_sat	1.1426282	down	0.0181	IGHG1	Immunoglobulin heavy constant gamma1
217039_xat	1.1115546	down	0.0336	IGHG1	Immunoglobulin heavy constant gamma1

Table 12. Chemokine and its receptor expression in Alzheimer's disease

ProbeSet	FoldChange	Direction	P value	Gene	Description
220565_at	1.1213491	down	0.01473	CCR10	chemokine (C-C motif) receptor 10
206978_at	1.2938806	up	0.001603	CCR2	chemokine (C-C motif) receptor 2
207794_at	1.1220208	up	0.042735	CCR2	chemokine (C-C motif) receptor 2
208376_at	1.134801	down	0.003293	CCR4	chemokine (C-C motif) receptor 4
211434_s_at	1.1275511	down	0.008782	CCRL2	chemokine (C-Cmotif) receptor-like 2
203687_at	1.1088936	down	0.009905	CX3CL1	chemokine (CX3C motif) ligand 1
204470_at	1.1264584	up	0.002264	CXCL1	chemokine (C-X-C motif) ligand 1
207681_at	1.1043607	down	0.00672	CXCR3	chemokine (C-X-C motif) receptor 3
209201_x_at	1.241918	up	3.98E-04	CXCR4	chemokine (C-X-C motif) receptor 4
211919_s_at	1.2920877	up	9.50E-05	CXCR4	chemokine (C-X-C motif) receptor 4
217028_at	1.3056723	up	0.001149	CXCR4	chemokine (C-X-C motif) receptor 4
206126_at	1.1033967	down	0.030718	CXCR5	chemokine (C-X-C motif) receptor 5

Table 13. TNF and its receptor up-regulation in Alzheimer's disease

ProbeSet	Fold	Direct	P value	Gene	Description
200704_at	1.160545	up	0.0408727	LITAF	LPS-induced TNF factor
214329_xat	1.1804326	up	0.0204381	TNFSF10	TNF(ligand) member10
209295_at	1.1786484	up	0.0264921	TNFRSF10B	TNF receptor superfamily10b
211163_sat	1.1980032	up	0.0393827	TNFRSF10C	TNF receptor superfamily10c
218368_sat	1.135739	down	0.0240022	TNFRSF12A	TNF receptorsuperfamily12A
207643_sat	1.1773607	up	0.0194878	TNFRSF1A	TNF receptor superfamily1A
203508_at	1.2001286	up	0.0051362	TNFRSF1B	TNF receptor superfamily1B
214228_xat	1.1537104	down	5.31E-04	TNFRSF4	TNF receptor superfamily4
202510_sat	1.222888	up	0.0041997	TNFAIP2	TNF, alpha-induced protein 2
208296_xat	1.2485156	up	0.0089159	TNFAIP8	TNF, alpha-induced protein 8
210260_sat	1.2693824	up	0.0100055	TNFAIP8	TNF, alpha-induced protein 8

Table 14. Apoptosis related gene up-regulation in Alzheimer's disease

ProbeSet	FoldChange	Direction	P value	Gene	Decription
Caspase-related					
209939_x_at	1.1977547	up	0.0083191	CFLAR	CASP8 and FADD-like
210563_x_at	1.1802275	up	0.0175538	CFLAR	CASP8 and FADD-like
206011_at	1.2169576	up	0.0215192	CASP1	caspase 1,
209970_x_at	1.1794986	up	0.0034734	CASP1	caspase 1,
211366_x_at	1.164994	up	0.0116157	CASP1	caspase 1,
211367_s_at	1.2773147	up	0.0203699	CASP1	caspase 1,
211368_s_at	1.2330801	up	0.0190248	CASP1	caspase 1,
205467_at	1.134219	up	5.83E-04	CASP10	caspase 10
211888_x_at	1.1168377	down	0.0470788	CASP10	caspase 10
209310_s_at	1.2395142	up	0.001984	CASP4	caspase 4
213596_at	1.2576379	up	0.0045759	CASP4	caspase 4
FAS					
204780_s_at	1.3957262	up	0.002561	FAS	Fas (TNF receptor 6)
215719_x_at	1.2370052	up	0.0044249	FAS	Fas (TNF receptor 6)
216252_x_at	1.1905588	up	0.0013671	FAS	Fas (TNF receptor 6)

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