Research Article

Unraveling the Role of TREM2 and CD33 in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by the accumulation of amyloid plaques and neurofibrillary tangles. This study investigates the role of two key genes, TREM2 and CD33, in AD pathogenesis. Gene expression profiles from human brain samples and transgenic mouse models were analyzed using data from the Gene Expression Omnibus. Differential gene expression analysis revealed significant upregulation of TREM2 and CD33 in AD samples compared to controls. Analysis of KEGG pathway, a database composed of biological pathway maps, showed TREM2 involvement in osteoclast differentiation and CD33 in hematopoietic cell lineage. String database analysis highlighted both genes' roles in regulating tumor necrosis factor production and cytokine production. Furthermore, TREM2 variants in AD patients were examined, identifying six variants (H157Y, R98W, D87N, T66M, Y38C, and Q33X) exclusive to AD samples. The R47H variant showed the strongest correlation with AD ($p<0.001$). The following SNPs of CD33 were identified as contributors to AD development: rs3826656, rs3865444, and rs12459419. These findings suggest that TREM2 and CD33 play crucial roles in AD progression, potentially through modulation of microglial function and inflammatory responses. These genes may serve as promising targets for developing novel AD therapeutics and biomarkers.

Keywords: Alzheimer's disease; TREM2; CD33; neurodegenerative; GEO2R

INTRODUCTION

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by the accumulation of amyloid plaques and neurofibrillary fibers (1). Patients with the disorder experience difficulty with memory, cognitive understanding, behavior, and daily functions. It is the leading cause of dementia, impacting more than 47 million individuals worldwide (roughly 60% of all dementia cases) (2). By 2050, the number of patients with AD will surpass 130 million (3). AD is typically divided into two categories: Familial Alzheimer's Disease (FAD) and Sporadic Alzheimer's Disease (SAD). Familial Alzheimer's Disease (FAD), also known as Early Onset AD (EOAD), accounts for 5% of all diagnosed cases and results from genetic inheritance (4). Sporadic Alzheimer's disease (SAD), also known as Late Onset AD (LOAD), accounts for the remaining patients and results from a combination of genetic and environmental factors, often developing later in life (2). Due to differences in the development and progression of the disorder, personalized treatment is unavailable, and no direct cause is confirmed. There are various risk factors associated with the development of AD; they include but are not limited to depression, environmental factors,

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smoking, and alcohol use. Currently, acetylcholinesterase inhibitors, memantine, and 3/anti-amyloid monoclonal antibodies are used to treat AD (2). Though effective, more research is required to expand on the scientific understanding of AD and discover ways to directly target the disorder.

METHODS

To further explore genes associated with AD, the Gene Expression Omnibus (5) was accessed to search for datasets that examine the differences in expression among genes in AD and control patients. The first dataset studied was GSE118553, which analyzed differential expression on microarray profiled human brains in regions of the brain affected by AD (6). The AD and control samples from the entorhinal cortex were input into GEO2R (7). The entorhinal region is one of the first areas of the brain affected by AD, and it is responsible for memory, navigation, and time perception (8). The second dataset studied was dataset GSE144459, which collected brain and blood samples from 3xTg-AD mice and B6129SF2 wild-type mice to find new biomarkers of AD and confirm the presence of previous biomarkers (9). 3xTg-AD mice are used in experimentation to examine plaque and neurofibrillary tangle pathology in AD (10). The samples from the brain's hippocampus region, a region involved in memory and affected by AD development, were input into GEO2R.

To better understand how the upregulation of TREM2 and CD33 could impact the development of AD, the KEGG pathway (11) in which each gene is involved was studied. Additionally, TREM2 and CD33 were inserted into the String database (12) to find biological processes associated with the genes, producing string maps. The String-db maps provide a detailed analysis of connections between genes closely associated with TREM2 and CD33 and include biological and KEGG pathways that they share.

RESULTS

The analysis of both datasets displayed upregulation of TREM2 and CD33 in AD samples. The volcano plots (Figure 1) display the differentially expressed genes in the datasets based on upregulation (red) and downregulation (blue). The p-value cutoff is 0.05, and upregulated genes have a positive log fold change, while downregulated genes have a negative log fold change. The UMAP plots (Figure 2) show the similarity of samples, and a general differential distribution of samples between AD and control was observed. In dataset GSE118553, TREM2

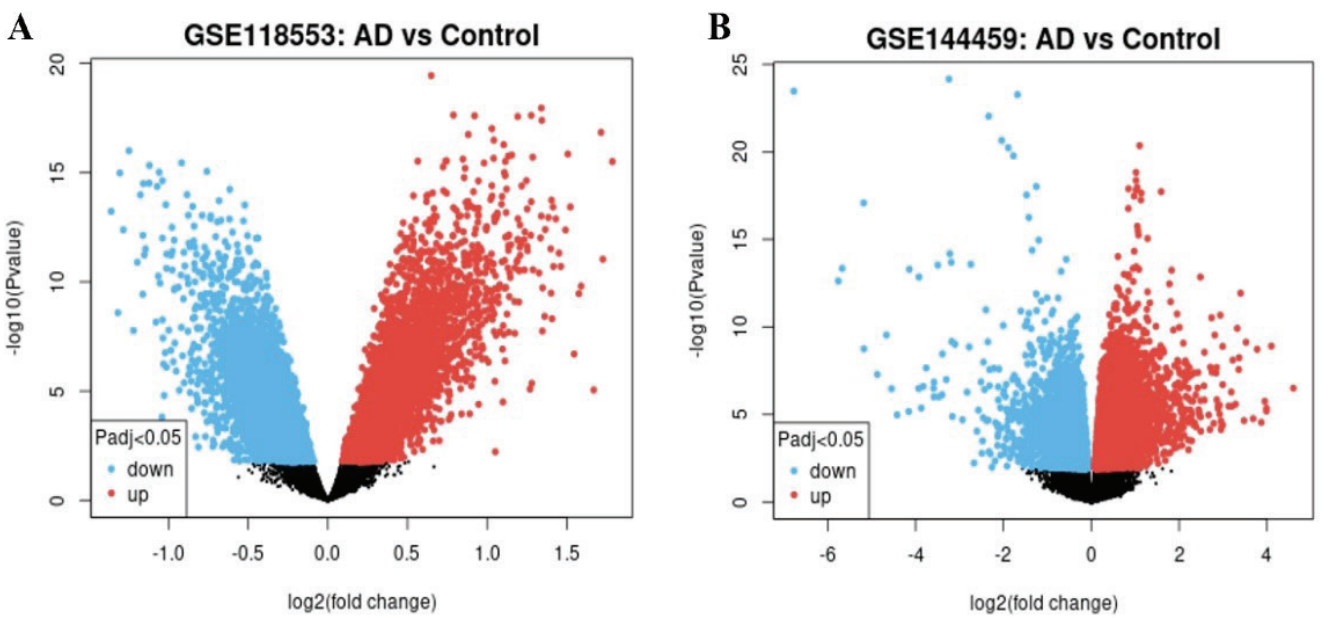

Figure 1. Volcano plots of differentially expressed genes. Upregulated genes are shown in red and downregulated genes in blue. The p-value cutoff is 0.05, with positive log fold change indicating upregulated and negative log fold change indicating downregulation (7).

has a p-value of 0.0000116 and a LogFC of 0.46604386, making it statistically significant and upregulated in the dataset. Similarly, in dataset GSE144459, TREM2 has a p-value of 0.000549 and a LogFC of 0.32404858, making it statistically significant and upregulated in the dataset. CD33 has a p-value of 0.00126 and a LogFC of 0.31369396, which makes it statistically significant and upregulated as well.

Based on the KEGG pathway analysis, TREM2 is involved in Osteoclast Differentiation which is responsible for bone resorption and is regulated by signaling pathways activated via Receptor Activator of Nuclear Factor – kappa B (RANK) and immune receptors (13). The gene is expressed by bone marrow macrophages (BMMs), and it works with its co-receptor, DAP12, to mediate signaling in immune cells and stimulate myeloid cell activation (14). These interactions result in cytokine production and release, migration, phagocytosis, and proliferation. Increased expression of TREM2 results in increased phosphorylation of DAP12, microglial phagocytosis, and promotion of chemokine migration (15). Microglial phagocytosis results in the uptake and secretion of pathogenic Aβ, which prevents the accumulation of amyloid plaques. In contrast, overexpression of soluble TREM2 may disrupt the blood-brain barrier, which leads to the leakage of sTREM2 into the cerebrospinal fluid. Elevated levels of sTREM2 in CSF may result in increased expression of proinflammatory proteins in the early stages of AD (16).

Furthermore, KEGG pathway analysis indicated that the CD33 gene is involved in Hematopoietic Cell Lineage (17), which produces blood cells from hematopoietic stem cells (HSC). It is associated with the processes occurring in bone marrow, which include the production of myeloid-related dendritic cells, macrophages, neutrophils, erythrocytes, and platelets. In the pathway, CD33 is expressed by "colony forming unit that generates myeloid cells" - GEMM: granulocyte, erythrocyte, monocyte, and megakaryocytic (CFU-GEMM) (18), which differentiates to produce red blood cells, white blood cells, and platelets. It is also expressed by BFU-E (burst-forming unit-erythroid), which is involved in erythropoiesis (19); burst-forming unit-megakaryocyte (BFU-MK); and colony-forming unit-granulocyte-macrophage (CFU-GM). CD33 is an inhibitory receptor that recruits Src homology (SH) 2 domain-containing proteins via its immunoreceptor tyrosine-based inhibitory motif (ITIM) domains. Increased expression of CD33 by macrophages and myeloid cells results in the prevention of cellular processes such as phagocytosis. Therefore, microglial clearance of pathogenic Aβ via phagocytosis is inhibited, accumulating amyloid plaques and leading to AD (20).

The String-db maps for TREM2 and CD33 (Figure 3) demonstrated that both genes are involved in regulating tumor necrosis factor production and the negative regulation of cytokine production. In the TREM2 String map, regulation of tumor necrosis factor production has a strength of 1.82 and a false discovery rate of 2.63e-06.

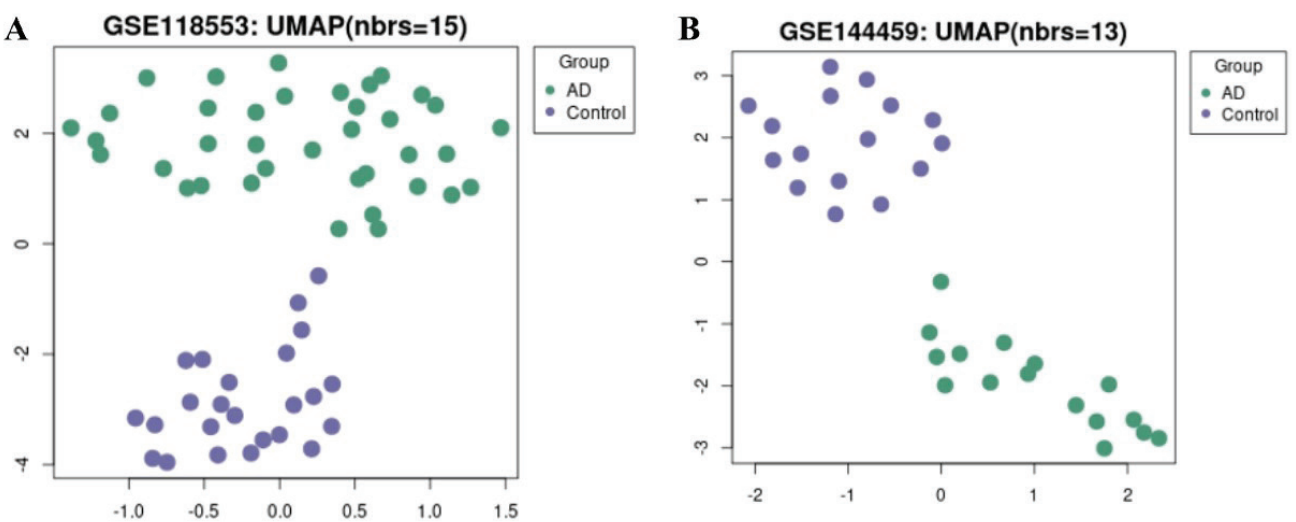

Figure 2. UMAP (Uniform Manifold Approximation and Projection) plot demonstrating the similarity of samples between AD and control groups. The plots show general differential distribution of samples between AD and control (7).

Negative regulation of cytokine production has a strength of 1.4 and a false discovery rate of 0.0026. In the CD33 String map, regulation of tumor necrosis factor production has a strength of 1.74 and a false discovery rate of 0.0003. Negative regulation of cytokine production has a strength of 1.4 and a false discovery rate of 0.0067. The strength of a pathway assesses how large the enrichment of the pathway is among the genes, and the false discovery rate displays the statistical significance of the enrichment (cutoff: <0.05). These statistics validate the significance of these biological processes in association with the TREM2 and CD33 genes. Tumor necrosis factor (TNF) is a cytokine involved in cell survival, proliferation, differentiation, and death (21). The negative regulation of cytokines prevents their production and inhibits the regulation of the immune responses. Neuroinflammation produces inflammatory cytokines, which signal the early progression of AD (22). The prevention of cytokine production can limit excess inflammation caused by the overexpression of cytokines (23).

DISCUSSION

TREM2 is a triggering receptor expressed on myeloid cells throughout the central nervous system, primarily in white matter (26). It encodes a membrane protein that makes a receptor-signaling complex with the TYRO binding protein, stimulating the activation of immune responses in macrophages and dendritic cells (27, 28).

In a study conducted by the NIH, experimenters analyzed the APP, PS1, PS2, PGRN, MAPT, and TREM2 genes in 281 AD and 504 control patients (29). Using PCR amplification and Sanger sequencing, they analyzed exon 2 of TREM2 in 811 AD patients and 603 control patients. Using previous studies and TaqMan SNP Genotyping Assays, the scientists also examined the single-nucleotide polymorphism rs75932628 (encodes the R47H variant) concerning the risk of AD (29). The final part of the experimentation tested TREM2 expression in a transgenic mouse model using TgCRND8 mice. The transgenic mice express a human APP695 transgene with two mutations (KM670/671NL and V717F); this gene appoints a transcript of APP, one of the genes associated with AD (29). The experiment results displayed six variants (H157Y, R98W, D87N, T66M, Y38C, and Q33X) found in AD samples, not control samples. The variant D87N was significantly associated with AD, having a p-value of 0.02. The Q33X, T66M, and Y38C variants were previously found in patients with dementia-like symptoms and study results show that they are more common in AD patients than unaffected individuals (p-value=0.01). The Q33X mutation potentially results in the loss of function of TREM2, so scientists suggest that T66M and Y38C variants could also contribute to the loss of function. From analysis of the SNP rs75932628, R47H showed the strongest correlation to AD (p-value<0.001). In examining the transgenic mouse model, the expression of TREM2 mRNA was increased in TgCRND8 mice, which

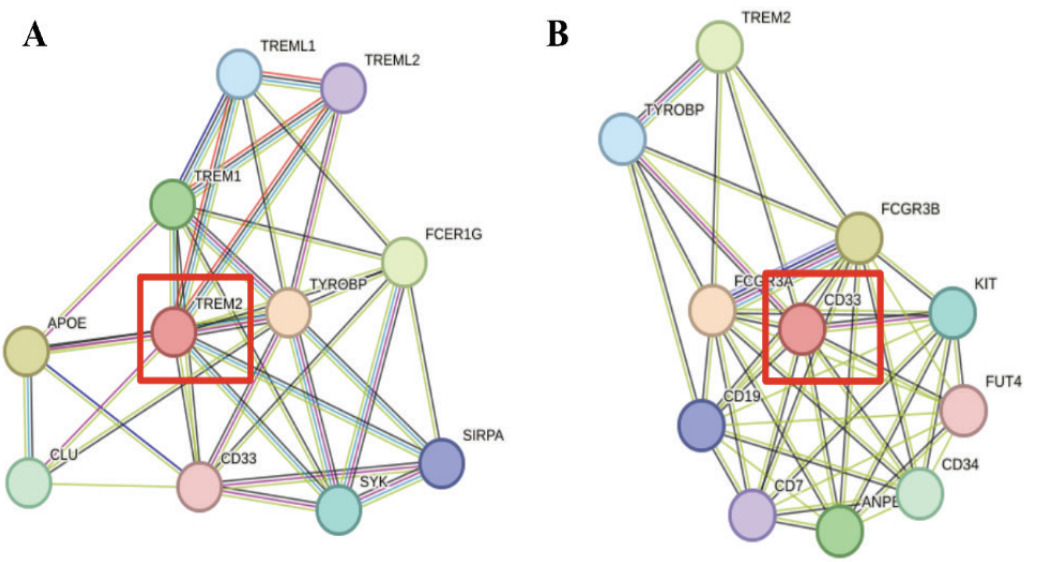

Figure 3. String maps of TREM2 and CD33 gene interactions, highlighting biological processes associated with both genes (24, 25).

contain the mutations in the APP695 transgene. Scientists also observed the upregulation of TREM2 in activated microglia and the expression of TREM2 in microglia surrounding the exterior of amyloid plaques (29).

Based on the results, heterozygous rare variants are linked to AD, and decreased expression of TREM2 could significantly decrease the pathogenic effect of the variants in AD. In microglia, TREM2 controls phagocytosis and inflammatory reactivity suppression, involving cytokine production and secretion repression (30). The upregulation of TREM2 could enhance phagocytic pathways, resulting in the removal of amyloid proteins in AD (30). Additionally, increased expression of TREM2 could result in the regulation of constitutive cytokine signaling, promoting survival via secretion of tumor necrosis factor. From this information, researchers can conclude that TREM2 rises with increased cortical levels of beta-amyloid and that the protein serves as a gateway for monitoring microglial responses (29).

CD33 is located on chromosome 19, and it contains seven exons; the regions composing this gene are the N-terminal signal peptide, the N-terminal Ig-like V-set domain, the C2-set domain, a transmembrane segment, and a cytoplasmic tail (31). It is a protein-coding gene that stimulates phosphatase and sialic acid binding activity. It is involved in processes such as negative regulation of cytokine production and positive regulation of protein tyrosine phosphatase activity. CD33 is located in the Golgi apparatus, on the external side of the plasma membrane, peroxisome, and various other cellular components (32).

In a series of Genome Wide Association Studies (GWAS), the rs3826656 SNP of CD33 contributed to the development of AD (33). Follow-up studies suggest the involvement of the rs3865444 SNP in AD development as well (34). Since CD33 is expressed by microglia in the brain (35, 36), this correlation may occur due to CD33 controlling microglial cell function. The allele rs12459419C is co-inherited with the rs3865444C allele and it affects the expression of hCD33M, an isoform of the CD33 gene (37). The co-inheritance of these two alleles leads to hCD33M:hCD33m transcript ratios of 9:1 instead of the AD-protective ratios of 7:3. hCD33M is the long isoform of the CD33 gene, while hCD33m is the short isoform (37). Co-localization of the long isoform with an activatory receptor causes the phosphorylation of the immunoreceptor tyrosine-based inhibitory motif (ITIM) of hCD33M. This action forms a landing site for phosphatases containing SH2 (Src homology 2), preventing inflammatory response. According to previous findings, there is increased expression of CD33M on microglia in the brains of AD patients. Increased expression of the long isoform results in decreased phagocytosis, while the short isoform increases phagocytosis. Decreased phagocytosis limits the uptake of amyloid plaques, resulting in their accumulation and the development of AD (38). In another series of Genome Wide Association Studies (GWAS), the blood CD33 mRNA level, serum CD33 protein level, and CD33 expression on immune cell subtypes were measured to examine the relationship between CD33 expression and AD (39). Scientists used MR, "a genetic method which applies genetic variants associated with the exposure as IVs to make causal inferences of the exposure on the outcome (40)" to conduct the studies. Results displayed that increased peripheral expression of CD33 is linked to AD development. Additionally, AD may not cause the elevation of CD33 in blood because the mRNA level and protein level of CD33 in the blood were found to be within the normal range in AD samples (39).

Identifying further treatment methods to ameliorate the severe symptoms of AD is crucial in improving patients' quality of life. A simple approach to limiting the effects of AD is increased and regular exercise, which will regulate microglial function via TREM2 modulation in the brain (41). An AD rat model displayed a connection between improved recognition memory and upregulation of the hippocampal TREM2/DAP12 pathway by limiting neuroinflammation (42). Similarly, an APP/PS1 mouse model showed that long-term running maintains levels of TREM2 protein and microglial metabolic activity (43). Other studies showed how exercise can increase dendritic spine density by regulating TREM2 expression (44), which is necessary for forming neuronal connections and signal transmission in the nervous system (45, 46). A study conducted to test the efficacy of gene therapy for CD33 in AD found that "injection of an adeno-associated virus (AAV) vector-based system encoding an artificial microRNA targeting *CD33* (miR^{CD33}) into *APP/PS1* mice reduced *CD33* mRNA and TBS-soluble Aβ40 and Aβ42 levels in brain extracts (47)." Early implementation of the treatment downregulated microglial receptor transcripts and pro-inflammatory activation genes, ultimately reducing AD pathology (47). This reduction in amyloid-beta levels could reduce the risk of AD development and lead to more successful treatment methods.

CONCLUSION

Alzheimer's disease is a neurodegenerative disorder affecting many individuals worldwide. The data from GEO2R, KEGG, String-db, and previous studies suggest

potential treatment options targeting the regulation of TREM2 and CD33 in AD patients. Treatment strategies by modulating these two genes could improve patient quality of life.

DECLARATION OF CONFLICT OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this article.

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