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CD33 and Alzheimer's Disease

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Abstract
Alzheimer's disease (AD), which is mainly characterized by impaired memory, is a rapidly growing clinical and public health issue due to the aging population. The neuropathological hallmarks of the disease include accumulation of senile plaques, composed of amyloid-beta, and neurofibrillary tangles. The amyloid-beta peptide (Aβ) cascade hypothesis suggests Aβ accumulation is the fundamental initiator and major pathogenic event for AD. Recent genome-wide association studies have illuminated cluster of differentiation 33 (CD33) is a new genetic risk factor for AD. CD33 as a type 1 transmembrane protein is mediating the cell–cell interaction. In the brain, CD33 is mainly expressed on microglial cells. In AD brain, the CD33 level is found to be positively correlated with amyloid plaque burden and disease severity.

Keywords: Alzheimer's disease, CD33, sialic acid, amyloid

INTRODUCTION

Alzheimer's disease (AD), which is the most common form of dementia, is a progressive neurodegenerative disorder. Alzheimer disease is currently no effective treatment and increasing prevalence and cost due to the aging population. The mechanisms underlying the onset and progression of the disease are incompletely understood [4]. Various disorders such as hypertension, diabetes, obesity, dyslipidemia and social and environmental factors such as head trauma, physical activity, diet, socioeconomic and educational level are risk factors for AD [16, 20, 8, 3]. AD is generally divided into two types, early and late onset. While late onset AD (LOAD) occurs after age 65, early onset AD (EOAD) occurs before age 65. Many studies have shown that LOAD and EOAD clinically distinct. While LOAD is characterized by impaired memory and visuospatial-language impairment [14], EOAD has a shorter life span and more aggressive progression [19]. Amyloid plaques and neurofibrillary tangles first described in a patient with strange behavior and a short memory defect by the German psychiatrist and neuropathologist Alois Alzheimer in 1906 [22]. In later studies; various pathological events clarified such as neuronal cell death, extracellular amyloid-beta accumulation, intracellular neurofibrillary tangles and microglial activation in the Alzheimer's brain [1]. The underlying causes of these multiple changes are unknown, but age, genetic factors and environmental factors are thought to play an important role [16, 4].

Relation between CD33 gene and AD

Many genes have been identified. In recent years Genome-Wide Association Studies (GWAS) have revealed new genetic risk factors for Alzheimer's: CD33, CLU, BIN1, PICALM, CR1, CD2Ap, EPHA1, ABCA7, MS4A4A / MS4A6E, SORL1, CLU and TREM2 [4, 21].

The cluster of differentiation 33 (CD33) gene (Figure 1), which is expressed in hematopoietic and phagocytic cells; are considered to be a new genetic risk factor associated with AD in GWAS [9, 6, 15, 5]. According to recent studies a strong association, especially between LOAD and CD33 gene, is reported [9].

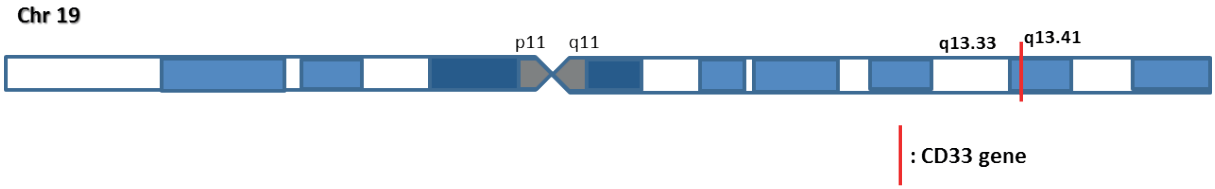

Figure 1. CD33 gene location [7]

It is shown single-nucleotide polymorphisms (SNPs) associated with LOAD are rs3865444, rs3826656 and rs114282264 (Figure 2). In some populations, such as Europe, North America and Korea, rs3865444 is a risk for AD (minor allele) while provided protective effects (T allele) against AD in other populations, such as Han Chinese population. Also it is suggested rs3865444 polymorphism is correlated with AD in Chinese, European, and North American populations [13]. The minor allele of rs3826656 risk factor for AD in a large family-based GWAS in European families. Nevertheless, in contrast to this finding, it is reported that the minor allele of rs3826656 was associated with a reduced risk of AD in Han Chinese population with apolipoprotein E (APOE) ε4 alleles [9]. But in a meta-analysis it is shown rs3826656 polymorphism is not in association with AD [10]. Recent studies have shown that a new SNP rs114282264 in the intron region of CD33 is significantly associated with AD in African Americans. However, this finding needs to be confirmed in other ethnic groups. It has also been shown that expression of CD33 is increased in microglia cells in Alzheimer's brain.

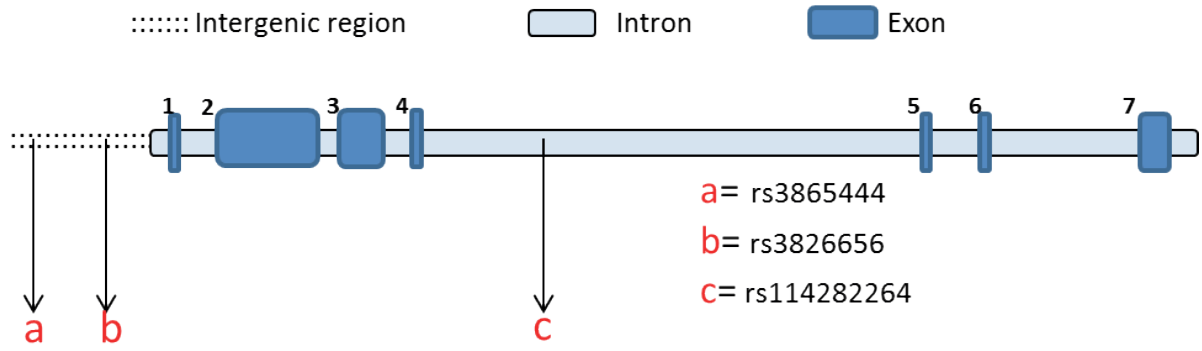

Figure 2. CD33 gene. SNPs in CD33 associated with AD are shown in the figure [9].

CD33 protein structure and location

CD33 gene is on the 19q13.33 chromosome and encodes the 67-kDa CD33 protein. CD33 protein which belongs to the sialic-acid-binding immunoglobulin-like lectins (SIGLECs) consists of an extracellular N-terminal V-set immunoglobulin domain responsible for sialic acid recognition, followed by a C2-type immunoglobulin repeat. Intracellularly, human CD33 which is expressed in mature monocytes, myeloid progenitor cells and macrophages has two cytoplasmic tyrosine-based motifs, these are immunoreceptor tyrosine-based inhibitory motif (ITIM) and ITIM-likemotif (Figure 3) [9, 23]. CD33 protein mediates cell-cell interaction and endocytosis and also it regulates cytokine secretion [23]. Additionally, CD33 inhibits immune cell functions and proinflammatory cytokines such as IL-1 [beta], TNF, IL-8. CD33 has been shown to regulate cell division and survival by inhibiting proliferation and inducing apoptosis [9]. Another important role of CD33 is able to bind to sialoglycans on target cells and interacts with sialylated pathogens and viruses which have self-synthesized sialoglycans on their surface. Because of this feature, CD33 could mediate endocytosis or, as opposed, could mediate spread their infection. In acute myeloid leukemia (AML) therapies CD33 is used as a target protein because of its phagocytic property.

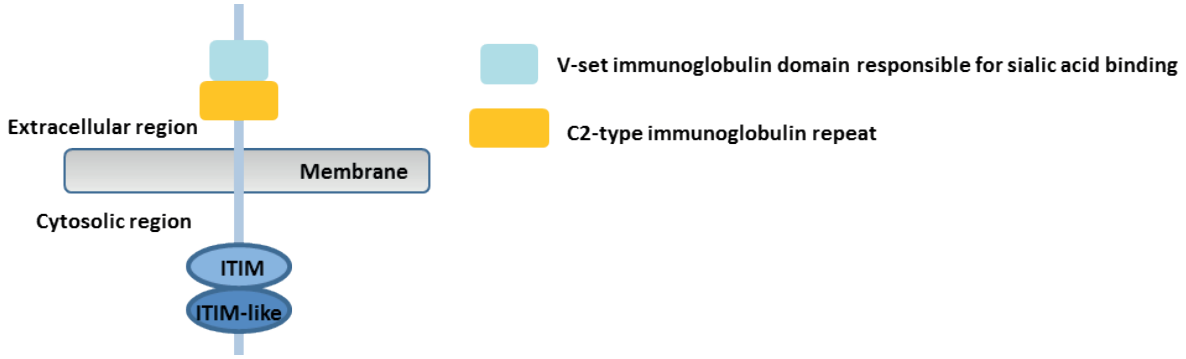

Figure 3. CD33 protein structure in Human [12].

CONCLUSION

High cognitive decline is caused elevated CD33 expression level in autopsy-confirmed AD patients' brain, is reported [11]. It is also shown CD33 is increased in AD brain, and it relates with amyloid protein and also disease patology [17]. Furthermore, it is suggested CD33 deficiency causes decreased AB in APP transgenic mice model [24]. CD33 mRNA level is increased due to upregulation of CD33 transcription in microglial cells. In another study, between CD33 mRNA level and Iba-1 (a biomarker of microglial cells), shown a significant correlation in brain tissues of AD cases [9].

CD33, a type 1 transmembrane protein, is expressed in brain macrophages and microglia cells, and has an inhibitory effect on Aβ uptake. Increased CD33 expression is associated with amount of plaque and so resulted increased disease severity [24, 2]. In addition to Aβ inhibition, the effect of CD33 on other biological mechanisms such as neuroinflammation and neuronal apoptosis should also be investigated. Additionally, pro-inflammatory cytokines in monocytes are shown to be inhibited by CD33. Further studies about relationship between CD33 plasma levels and disease must be done. CD33 SNPs in multiple ethnic populations are shown to be associated with LOAD. CD33 SNP rs3865444 protects against AD and reduces CD33 expression. It is also shown rs3865444 and rs114282264 are correlated with AD [18, 9]. More extensive genetic screening should be done to reveal other variants of CD33 associated with LOAD. These loci can be utilized as biomarkers for AD [18]. AD, is a progressive neurodegenerative disease, has been increasing its social and economic burden for both the individual and the society. Therefore, further studies are needed to elucidate the pathophysiology and genetics of the disease, and to develop novel therapeutics for the prevention and treatment of AD.

REFERENCES

[1] Barbagallo, M., Marotta F., Dominguez L.J. 2015. Oxidative stress in patients with Alzheimer's disease: effect of extracts of fermented papaya powder. Mediators of inflammation, Article ID 624801, volume 2015, http://dx.doi.org/10.1155/2015/624801.

[2] Efthymiou, A.G., Goate A.M. 2017. Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk, Molecular Neurodegeneration, 12:43.

[3] Gatz, M., Reynolds C.A., Fratiglioni L., Johansson B., Mortimer J.A., Berg S., Fiske A., Pedersen N.L. 2006. Role of genes and environments for explaining Alzheimer disease. Archives of General Psychiatry, 63(2), 168-174.

[4] Griciuc, A., Serrano-Pozo A., Parrado A.R., Lesinski A.N., Asselin C.N., Mullin K., Hooli B., Choi S.H., Hyman B.T., Tanzi R.E. 2013. Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron, 78(4): 631-643.

[5] Hollingworth, P., Harold D., Sims R., Gerrish A., Lambert J.C., Carrasquillo M.M., Abraham R., Hamshere M.L., Pahwa J.S., Moskvina V. et.al. 2011. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nature genetics, 43(5), 429-435.

[6] Hu, N., Tan M.S., Sun L., Jiang T., Wang Y.L., Tan L., Zhang W., Yu J.T., Tan L. 2014. Decreased expression of CD33 in peripheral mononuclear cells of Alzheimer's disease patients. Neuroscience letters, 563:51-54.

[7] Human Gene Database, Gene Cards, CD33 gene, https://www.genecards.org/cgi-bin/carddisp.pl?gene=CD33

[8] Imtiaz, B., Tolppanen A.M., Kivipelto M., Soininen H. 2014. Future directions in Alzheimer's disease from risk factors to prevention. Biochemical Pharmacology, 88(4):661-670.

[9] Jiang, T., Yu J.T., Hu N., Tan M.S., Zhu X.C., Tan L. 2014. CD33 in Alzheimer's Disease. Molecular Neurobiology, 49:529-535.

[10] Jiang, Y.T., Li H.Y., Cao X.P., Tan L. 2018. Meta-analysis of the association between CD33 and Alzheimer's disease, Annals of translational medicine, 6(10).

[11] Karch, C.M., Jeng A.T., Nowotny P., Cady J., Cruchaga C., Goate A.M. 2012. Expression of Novel Alzheimer's Disease Risk Genes in Control and Alzheimer's Disease Brains, PLoS One, 7(11).

[12] Laing, A.A., Harrison C.J., Gibson B.E.S., Keeshan K. 2017. Unlocking the potential of anti-CD33 therapy in adult and childhood acutemyeloid leukemia, Experimental Hematology, Volume 54:40-50.

[13] Li, X., Shen N., Zhan S., Liu J., Jiang Q., Liao M., Feng R., Zhang L., Wang G., Ma G., Zhou H., Chen Z., Jiang Y., Zhao B., Li K., Liu G. 2015. CD33 rs3865444 polymorphism contributes to Alzheimer's disease susceptibility in Chinese, European, and North American populations. Molecular neurobiology, 52(1), 414-421.

[14] Licht, E.A., Mcmurtray A.M., Saul R.E., Mendez M.F. 2007. Cognitive Differences between Early and Late-Onset Alzheimer's Disease. American Journal of Alzheimer's Disease & Other Dementias, 22(3):218-222.

[15] Mao, Y.F., Guo Z.Y., Pu J.L., Chen Y.X., Zhang B.R. 2015. Association of CD33 and MS4A cluster variants with Alzheimer's disease in East Asian populations, Neuroscience letters, 609:235–239

[16] Mayeux, R., Stern Y. 2012. Epidemiology of Alzheimer Disease. Cold Spring Harbor perspectives in medicine, 2(8): 1-18.

[17] Mirandei, J.V.H., Audrain M., Fanutza T., Kim S.H., Klein W.L., Glabe C., Readhead B., Dudley J.T., Blitzer R.D., Wang M., Zhang B., Schadt E.E., Gandy S., Ehrlich M.E. 2017. Defciency of TYROBP, an adapter protein for TREM2 and CR3 receptors, is neuroprotective in a mouse model of early Alzheimer's pathology, Acta Neuropathol 134:769–788.

[18] Misra, A., Chakrabarti S.S., Gambhir I.S. 2018. New genetic players in late-onset Alzheimer's disease: Findings of genome-wide association studies, Indian J Med Res 148, 135-144.

[19] Panegyres, P.K., Chen H.Y. 2013. Differences between early and late onset Alzheimer's disease, American journal of neurodegenerative disease, 2(4):300-306.

[20] Reitz, C., Mayeux R. 2014. Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. Biochemical Pharmacology, 88: 640–651.

[21] Rosenberg, R.N., Lambracht-Washington D., Yu G., Xia W. 2016. Genomics of Alzheimer disease: a review. JAMA neurology, 73(7), 867-874.

[22] Selekler, K. 2010. Alois Alzheimer ve Alzheimer hastalığı. Türk Geriatri Dergisi, 13(3): 9-14.

[23] Wang, M.M., Miao D., Cao X.P., Tan L., Tan L. 2018. Innate immune activation in Alzheimer's disease, Annals of translational medicine, 6(10):177.

[24] Wes, P.D., Sayed F.A., Bard F., Gan L. 2016. Targeting microglia for the treatment of Alzheimer's Disease. Glia, 64(10), 1710-1732.