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Genetic predisposition to Alzheimer's disease

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ABSTRACT

Introduction: Alzheimer's disease is the most common neurodegenerative condition. It is caused by a number of factors, one of them being a genetic predisposition. Genome-wide association studies identify candidate genes whose changes could contribute to the development of this disease.

Aim: This literature review summarizes the findings of genome-wide association studies establishing the genetic predisposition to late-onset Alzheimer's disease. It aims to compile an overview of candidate genes associated with this disease for future research.

Methodology: This article is a literature review. It describes important genes associated with late-onset Alzheimer's disease.

Findings: Based on previous experience, the genes *APOE, TOMM40, CD36, CLU, CHAT, IDE* and *TNK1* were selected. They are the most suitable candidates for future targeted genetic testing of the Czech population.

Conclusions: The article presents a list of genes associated with late-onset Alzheimer's disease. Future research in this area can significantly enhance the prediction and subsequent prevention of this serious disease.

KEY WORDS

Alzheimer's Disease, genes, *APOE, TOMM40, CD36, CLU, CHAT, IDE, TNK1*

LITERATURE OVERVIEW QUESTION

Genetic predisposition is a significant risk for Alzheimer's disease, which is the most common form of dementia. As the number of dementia patients continues to increase sharply around the world, much more research in this area needs to be conducted. Genetic factors play a key role in early diagnosis and application of the principles of prevention.

BACKGROUND

Alzheimer's disease (AD), which is the most common form of dementia, causes a gradual decline in cognitive functions, including memory, thinking, and planning. The disease is divided into early-onset AD and late-onset AD based on the age at which AD is diagnosed. Early-onset AD typically starts prior to the age of 65, and family history of the condition is an important factor. A far more common is late-onset AD, which does not correlate with familial aggregation. This may be, however, due to a lack of information about the family history of the disease in older people. Given that the genetic risk for late-onset AD is comparable to risks observed, for example, in Parkinson's disease or schizophrenia, genetic predisposition is bound to also play a role here. Genome-wide association studies (GWAS) have sought for many years to identify genes which contribute to the increased risk of AD (1). Although GWAS have discovered many single nucleotide polymorphisms (SNPs) in genes, the number of studies summarizing findings about patients with late-onset ACH is low (2). This article reviews the results this method has produced within the Czech population.

DESCRIPTION OF THE RESEARCH STRATEGY

Data for this literature review were drawn from the latest professional publications and studies on genetic research, including studies the authors have participated in.

LITERATURE OVERVIEW

APOE

Apolipoprotein E (ApoE) is central to lipid metabolism and is often associated with neurodegenerative diseases such as AD. The protein serves mainly as a lipid transporter among various cells and tissues (3). It consists mainly of astrocytes in the central nervous system (5). With regard to AD, carrying the ε4 allele of the *ApoE* gene is a major genetic risk factor for late-onset AD (4). There are three main alleles of the *ApoE* gene, where *ApoE-ε3* is considered a common allele, while the remaining alleles *ApoE-ε2* and *ApoE-ε4* have amino acid substitutions at positions 112 and 158 in the protein chain (3). Special attention is paid to ApoE-*ε4* in connection with neurodegenerative diseases (3). Mouse models have showed that *ApoE-ε4* has a specific impact on the integrity of hematoencephalic barrier (6). In addition, animal studies and human studies demonstrate that brain Aβlevels and the amyloid plaque load depend on *ApoE* in the sense that *ApoE-ε4* is less effective in Aβ removal compared to the other alleles (7). Epidemiologic and genetic studies document that carriers of *ApoE- ε4* are twice to three times more likely to develop AD (8,7,5). In addition, people with two copies of this allele are up to twelve times more likely to develop AD (8). The *ApoE-ε2* allele, in contrast, tends to have protective effects (8,7,5). It is also suggested that the impact of the *ApoE-ε4* allele is stronger in women compared to men (9). Furthermore, another association between *ApoE-ε4* and AD has been established. Carriers of the *ApoE-ε4* allele are usually diagnosed with the disease at a younger age (5). A study examining *ApoE* levels in cerebrospinal fluid did not, however, find any association with cognition, and patients with AD did not differ from healthy controls. An interesting finding was that the carriers of *ApoE-ε4* had significantly lower plasma levels of *ApoE*, which could be due to a specific decrease in the concentration of the *ApoE-ε4* isoform (4). In addition, research using a large sample of patients from China with AD demonstrated that *ApoE* can be a strong predictor of conversion from mild cognitive impairment (MCI) to AD (10). In line with previous studies it was suggested that the risk of conversion from MCI to AD is greater among female carriers of the *ApoE-ε4* allele (11). The results indicate that a greater understanding of the interactions between *ApoE* and gender could provide new insights into its role in the pathogenesis of AD (12).

TOMM40

The *TOMM40* gene is another candidate gene studied in connection with AD (13). The *ApoE* and *TOMM40* genes, in addition, are in linkage disequilibrium (14), which is why a synergistic effect is also considered (15). *TOMM40* encodes a protein which is a part of the translocase of the outer mitochondrial membrane (Tomm). It is a subunit which forms the channel of the Tom complex and imports protein precursors into mitochondria. Aβ peptides are thought to interfere with mitochondrial proteins during the import and thus disrupt mitochondrial function, which contributes to the observed pathology of AD (16). GWAS was used to identify several SNPs which are significantly associated with an increased risk of AD. A meta-analysis has confirmed that the rs2075650 polymorphism is associated with AD across different populations (13). The SNPs rs157580 and rs11556505 in the *TOMM40* gene have also been linked to AD (17). Furthermore, research on the expression of *TOMM40* in blood has concluded that the expression of this gene is lower among patients with AD compared to subjects of the same age without AD (18). Some studies have also observed that *TOMM40* may affect AD onset age (14). For example a study on the rs10524523 polymorphism, which is a polymorphic poly-T variant in the *TOMM40* gene, has found that the carriers of *ApoE-ε3* and multiple poly-T repeats, develop AD 7 years earlier on average compared to carriers of the same *ApoE* allele in combination with short poly-T repeats (15). However, a follow-up study, aimed to confirm the results did not reach the same conclusion. Although an association between the carriers of *ApoE-ε3* was observed, it was contrary to the previous study. Furthermore, no association was established with the expression of *TOMM40*, *ApoE* or the levels of Aβ and tau protein in cerebrospinal fluid (19). Further research into the relationship between *TOMM40*, *ApoE,* and the risk of AD is needed.

CD36

The *CD36* gene encodes a membrane glycoprotein which plays a role in fat taste perception, glycolipid metabolism, and contributes to the development of atherosclerosis (20). *CD36* is also involved in intracellular signalling, immunity, and metabolic processes, and, based on *in vitro* studies (21, 22) it is able to bind Aβ. In addition, *CD36* is thought to cause pro-inflammatory reactions common among patients with AD (23). Furthermore, some SNPs in the *CD36* gene

have been associated with obesity, which in itself contributes to an increased AD risk (24). This was also confirmed in the Czech population when a link was discovered between polymorphism in the *CD36* gene, linolenic acid detection, and higher body weight (25). Another observation is that the A allele in the SNP rs3211892 in the *CD36* gene significantly increases the risk of AD (26). One of the studies also investigated the expression of *CD36* in the leukocytes of patients with AD, an MCI group, and control subjects. The results suggest that *CD36* expression was significantly reduced in patients with AD and MCI compared to controls. This means that decreased expression of this gene in leukocytes could serve as a marker to identify patients at increased risk of these diseases (23).

CLU

The *CLU* gene encodes clusterin, which is also termed the apolipoprotein J. The gene is assumed to contribute to the pathogenesis of AD, and the assumption is based on strong evidence. Clusterin binds Aβ oligomers and can prevent their fibrilarization. It also works as a complement inhibitor, thus preventing the activation of the complement system, which is often activated in patients with AD. As clusterin is also a lipoprotein particle, it can affect cholesterol transport, similarly to *ApoE*. However, it can also function as a stress-induced chaperone, inhibiting neuronal apoptosis (27). Based on GWAS, the C allele in the rs11136000 polymorphism in the *CLU* gene may contribute to the development of AD. This allele is detected in 88% of the Caucasian population. The white cortex of young adults with the high-risk C allele was found to have lower fractional anisotropy. This supports the view that *CLU* may cause local vulnerability important for the onset of the disease (28). Yet another study indicates that carrying the high-risk C allele is associated with faster longitudinal ventricular expansion in the brain, which is independent of *ApoE* genotype or dementia status (29). The effect of the rs11136000 polymorphism was also verified on the Chinese population. No statistically significant association was found between patients with AD and the control group. The study, however, identified a different *CLU* polymorphism rs9331888, whose G minor allele strongly associated with AD (27). Another study focused on the relationship between rs9331888 and AD described their strong association in the Caucasian population. The association was nonetheless not confirmed in East Asia. (30). This statement was confirmed by a meta-analysis (31). The results of another meta-analysis nevertheless suggest that the rs11136000 polymorphism is associated with AD risk, and the risk is consistent both for the Caucasian and the Asian population (32). Research was also conducted into the influence of genetic variants in *CLU* on neuroimaging markers in healthy controls, patients with MCI and with AD. The research established a significant association for 4 locuses (rs11136000, rs1532278, rs2279590, rs7982) with Aβ deposits, and the rs9331888 polymorphism correlated with an increase in the deposits (33). These observations suggest that *CLU* SNPs contribute to AD susceptibility (30).

CHAT

Choline acetyltransferase (ChAT), the enzyme responsible for acetylcholine synthesis, is encoded by the *CHAT* gene (34). *CHAT* expression is typical of brain cholinergic neurons, and cholinergic signalling is known to be vital for learning and memory (35). It is also possible that SNPs in *CHAT* affect ChAT activity, and this is the cause of the abnormal behaviour typical of AD (36). Based on this assumption, a cholinergic hypothesis was proposed, predicting that cholinomimetics could improve cholinergic functions. The assumption, however, was proven to be incorrect (37). On the other hand, deterioration of cholinergic function is an integral part of AD, and understanding the role of *CHAT* in relation to AD may improve therapeutic outcomes. For example, the rs3810950 polymorphism in *CHAT* has been found to be related to cognitive abilities. Research was carried out among university students from China, and the results suggest that the A allele of this polymorphism may reduce ChAT levels in cholinergic neurons, which results in a cognitive deficit (36). A study of the Czech population confirmed that the rs3810950 polymorphism contributes to an increased risk of AD (38). Research also demonstrated that the rs3810950 polymorphism may affect the age of AD onset, as patients with the AA genotype were diagnosed with AD at a statistically lower age (39). A meta-analysis validated association between rs3810950 and AD and identified rs2177369 as another statistically significant polymorphism associated with this disease. A stratification analysis also revealed an interaction between the *ApoE* genotype and polymorphisms in *CHAT*, which could be an important risk factor for AD (40). Another study looked at the relationship between polymorphisms in *CHAT* and the structure of the parahipocampus and hippocampus. It found that SNP rs12246528 was associated in a parahipocampal structure, while a smaller volume, surface area, and thickness of this structure were observed in the A allele carriers. Hippocampal volume showed the strongest association for SNP rs1917814, where the T allele was associated with

a larger volume. Furthermore, the SNP rs3729496 was found to correlate with memory range. As this study has covered the Chinese population only, a similar analysis across different populations is needed (41). In summary, the association between *CHAT* and AD is supported by multiple investigations, and therefore the gene is highly likely to play a role in the development of AD.

IDE

Genes tested for potential effects on AD development include the *IDE* gene, which encodes an insulin degrading enzyme (42). This zinc metalloproteinase cleaves several peptides, such as glucagon, insulin, β-endorphin, and the intracellular domain of APP (43). The enzyme is also able to degrade Aβ *in vitro*, which could affect the course of AD (42). This view is supported by the fact that patients with AD were found to have reduced levels of this protein and mRNA (44). It was observed in connection with this finding that an increased *IDE* expression generated lower plasma concentrations of Aβ, which lowers AD risk (45). Multiple association studies investigate the relationship between various *IDE* SNPs and AD risk across different populations. For example, in the Chinese population, this association was found for the SNP rs3781239. A meta-analysis determined that the SNP rs1832196 was significantly associated with AD, while no association was observed for rs3758505 (46). Although another study reported a weak association between AD and *IDE*, the association was consistent across samples from a range of ethnic groups, suggesting that *IDE* may be a causal agent for AD (47). Yet, contrary to the other studies, one study detected elevated levels of insulin degrading enzyme among patients with AD (48). Further research into whether the insulin degrading enzyme can provide new insights into AD or contribute to its treatment is therefore needed (49).

TNK1

The gene encoding non-receptor tyrosine kinase 1 was associated with AD based on GWAS (50). This gene was discovered as a tumour suppressor gene, which plays a role in the intracellular transduction pathway as well as in TNF-α induced apoptosis. Recent research also suggests that *TNK1* promotes the survival and growth of pancreatic tumour cells (51). However, signalling pathways regulated by *TNK1* continue to be largely unknown (52). One of the most studied AD-associated SNPs in *TNK1* is rs1554948 (50). A study found that the A allele of rs1554948 was more common among the elderly without cognitive decline and its prevalence grew with age, while the prevalence of this allele decreased with age in patients with AD (51). A meta analysis included all available data on SNP rs1554948 from other studies as well as its own data. The latter, when analyzed separately, did not show significant association with AD. Yet, once included in the meta-analysis, the polymorphism remained statistically significant (53). The fact that *TNK1* is an integrated component of the interferon signalling pathway is of significance in this context. *TNK1* has been observed to have a marked effect on liver sensitivity to hepatitis C virus and also to affect the response to interferon-based antiviral therapy (52). The ability of *TNK1* to modulate immune functions may be one of the ways in which this gene contributes to the progression of AD (51).

RESULTS

Alzheimer's disease is a multifactorial condition caused by a great number of external and internal factors. Given that no new drug treating AD has been developed for years, in spite of intensive efforts, research is now focused mainly on prevention.

APOE, TOMM40, CD36, CLU, CHAT, IDE and *TNK1* have been found to associate within the Czech population with an increased risk of AD. These results could be used to build a panel of genetic tests and the genetic results to calculate potential risk of late-onset AD, once incorporating the lifestyle data of the subjects. The data could contribute to preventive measures, which could delay the onset of AD.

The pathogenesis of AD is an intricate complex of processes and it cannot be said that the genetic polymorphisms under study are the principal cause of AD. External factors also play a role in the development of the disease. Frequently reported contributors include a variety of comorbidities, such as diabetes mellitus and cardiovascular diseases. Several studies also examined exposure to chemicals in relation to the development of late-onset AD (54, 55). Likewise, lifestyle factors such as smoking (56), alcohol consumption (57), and mental and physical activity (58, 59) modulate the risk of late-onset AD. If these factors are combined with the knowledge of how said genes are linked to the possible development of Alzheimer's disease, it will be possible to identify patients at increased risk of late-onset AD and thus contribute to the prevention of this serious disease.

REFERENCES

1. Lambert JCH, Amouyel P. Genetics of Alzheimer's disease: new evidences for an old hypothesis? Current opinion in genetics & development. 2011;21(3):295-301.

2. Alagiakrishnan K, Gill SS, Fagarasanu A. Genetics and epigenetics of Alzheimer's disease. Postgraduate medical journal. 2012;88(1043):522-529.
3. Huang Y, Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. Neurobiology of disease. 2014;72:3-12.
4. Martínez-Morillo E, et al. Total apolipoprotein E levels and specific isoform composition in cerebro-spinal fluid and plasma from Alzheimer's disease patients and controls. Acta neuropathologica. 2014;127(5):633-643.
5. Liu Ch, et al. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nature Reviews Neurology. 2013;9(2):106-118.
6. Bell RD, et al. Apolipoprotein E controtrols cerebrovascular integrity via cyclophilin A. Nature. 2012;485(7399):512-516.
7. Castellano, JM, et al. Human apoE isoforms differentially regulate brain amyloid-β peptide clearance. Science translational medicine. 2011; 3(89):89ra57.
8. Michaelson DM. APOE ε4: The most prevalent yet understudied risk factor for Alzheimer's disease. Alzheimer's & Dementia. 2014;10(6):861-868.
9. Kulminski AM, et al. Age, gender, and cancer but not neurodegenerative and cardiovascular diseases strongly modulate systemic effect of the Apo-lipoprotein E4 allele on lifespan. PLoS genetics. 2014;10(1):e1004141.
10. Wang PN, et al. APOE ε4 increases the risk of progression from amnestic mild cognitive impair-ment to Alzheimer's disease among ethnic Chinese in Taiwan. Journal of Neurology, Neurosurgery & Psychiatry. 2011;82(2):165-169.
11. Altman A, et al. APOE genotype by gender interaction revealed in CSF biomarkers and clinical conversion rates in the ADNI database. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2013;9(4):P245-P246.
12. Ungar L, Altmann A, Greicius MD. Apolipoprotein E, gender, and Alzheimer's disease: An overlooked, but potent and promising interaction. Brain imaging and behavior. 2014;8(2): 262-273.
13. Huang H, et al. The TOMM40 gene rs2075650 polymorphism contributes to Alzheimer's disease in Caucasian, and Asian populations. Neuroscience letters. 2016;628:142-146.
14. Ferencz B, Karlsson S, Kalpouzos G. Promising genetic biomarkers of preclinical Alzheimer's disease: the influence of APOE and TOMM40 on brain integrity. International Journal of Alzheimer's Disease. 2012;2012:421452.
15. Roses AD, et al. A TOMM40 variable-length polymorphism predicts the age of late-onset Alzheimer's disease. The pharmacogenomics journal. 2010; 10(5):375-384.
16. Zeitlow K, et al. The biological foundation of the genetic association of TOMM40 with late-onset Alzheimer's disease. Biochimica et Bio-physica Acta (BBA)-Molecular Basis of Disease. 2017; 1863(11):2973-2986.
17. Potkin SG, et al. Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's disease. PloS one. 2009;4(8): e6501.
18. Goh LK, et al. OMM40 alterations in Alzheimer's disease over a 2-year follow-up period. Journal of Alzheimer's Disease. 2015;44(1):57-61.
19. Cruchaga C, et al. Association and expression analyses with single-nucleotide polymorphisms in TOMM40 in Alzheimer disease. Archives of neurology. 2011;68(8):1013-1019.
20. Gong QW, et al. CD36 Gene Polymorphisms Are Associated with Intracerebral Hemorrhage Susceptibility in a Han Chinese Population. BioMed research international. 2017;2017:5352071.
21. Moore Kathryn J, et al. A CD36-initiated signaling cascade mediates inflammatory effects of β-amyloid. Journal of Biological Chemistry, 2002; 277:47373-47379.
22. Medeiros Lea A, et al. Fibrillar amyloid protein present in atheroma activates CD36 signal transduction. Journal of Biological Chemistry, 2004;279:10643-10648.
23. Giunta M, et al. The leukocyte expression of CD36 is low in patients with Alzheimer's disease and mild cognitive impairment. Neurobiology of aging. 2007;28(4):515-518.
24. Daoudi H, et al. Oral fat sensing and CD36 gene polymorphism in Algerian lean and obese teenagers. Nutrients. 2015;7(11):9096-9104.
25. Plesník J, et al. The rs1527483, but not rs3212018, CD36 polymorphism associates with linoleic acid detection and obesity in Czech young adults. British Journal of Nutrition. 2018; 119(4):1-7.
26. Šerý O, et al. CD36 gene polymorphism is associated with Alzheimer's disease. Biochimie. 2017135:46-53.
27. Yu JT, et al. Implication of CLU gene polymorphisms in Chinese patients with Alzheimer's disease. Clinica Chimica Acta. 2010; 411(19):1516-1519.
28. Braskie MN, et al. Common Alzheimer's disease risk variant within the CLU gene affects white matter microstructure in young adults. Journal of Neuroscience. 2011;31(18):6764-6770.

29. Roussotte FF, et al. Combined effects of Alzheimer risk variants in the CLU and ApoE genes on ventricular expansion patterns in the elderly. Journal of Neuroscience. 2014;34(19):6537-6545.
30. Zhang S, et al. CLU rs9331888 polymorphism contributes to Alzheimer's disease susceptibility in Caucasian but not East Asian populations. Molecular neurobiology. 2016;53 (3):1446-1451.
31. Shuai P, et al. Genetic associations of CLU rs9331888 polymorphism with Alzheimer's disease: a meta-analysis. Neuroscience letters. 2015; 591:160-165.
32. Liu G, et al. The CLU gene rs11136000 variant is significantly associated with Alzheimer's disease in Caucasian and Asian populations. Neuromolecular medicine. 2014;16(1):52-60.
33. Tan L, et al. The CLU gene rs11136000 variant is significantly associated with Alzheimer's disease in Caucasian and Asian populations. Neuromolecular medicine. 2014:16(1):52-60.
34. Shin K, et al. Human neural stem cells overexpressing choline acetyltransferase restore unconditioned fear in rats with amygdala injury. Behavioural Neurology. 2016;2016:8521297.
35. Soreq H. Checks and balances on cholinergic signaling in brain and body function. Trends in neurosciences. 2015;38(7):448-458.
36. Liu X, et al. Polymorphic variation in CHAT gene modulates general cognitive ability: an association study with random student cohort. Neuroscience letters. 2016;617:122-126.
37. Francis PT, et al. The cholinergic hypothesis of Alzheimer's disease: a review of progress. Journal of Neurology, Neurosurgery & Psychiatry. 1999; 66(2):137-147.
38. Hálová A, et al. CHAT gene polymorphism rs3810950 is associated with the risk of Alzheimer's disease in the Czech population. Journal of biomedical science. 2018;25(1):41.
39. Mengel-from J, et al. Genetic variants in the choline acetyltransferase (ChAT) gene are modestly associated with normal cognitive function in the elderly. Genes, Brain and Behavior, 2011;10(8):876-882.
40. Liu Y, et al. Genetic Association of CHAT rs3810950 and rs2177369 Polymorphisms with the Risk of Alzheimer's Disease: A Meta-Analysis. Bio-Med research international. 2016;2016:9418163.
41. Zhu B, et al. The Choline Acetyltransferase (CHAT) Gene is Associated with Parahippocampal and Hippocampal Structure and Short-term Memory Span. Neuroscience, 2018;369:261-268.
42. Blomqvist MEL, et al. Sequence variants of IDE are associated with the extent of β-amyloid deposition in the Alzheimer's disease brain. Neurobiology of aging. 2005;26(6):795-802.
43. Cui PJ, et al. The association between two single nucleotide polymorphisms within the insulin-degrading enzyme gene and Alzheimer's disease in a Chinese Han population. Journal of Clinical Neuroscience. 2012;19(5):745-749.
44. Vepsäläinen S, et al. Combined risk effects of IDE and NEP gene variants on Alzheimer disease. Journal of Neurology, Neurosurgery & Psychiatry. 2009;80(11):1268-1270.
45. Kurochkin IV, et al. Toward allosterically increased catalytic activity of insulin-degrading enzyme against amyloid peptides. Biochemistry. 2016;56(1):228-239.
46. Zhang Y, et al. Meta-analysis of the insulin degrading enzyme polymorphisms and susceptibility to Alzheimer's disease. Neuroscience letters. 2013;541:132-137.
47. Mueller JC, et al. Weak independent association signals between IDE polymorphisms, Alzheimer's disease and cognitive measures. Neurobiology of aging. 2007;28(5):727-734.
48. Miners, JS et al. Neprilysin and insulin-degrading enzyme levels are increased in Alzheimer disease in relation to disease severity. Journal of Neuropathology & Experimental Neurology. 2009; 68(8):902-914.
49. Zhang H, et al. Characteristics of Insulin-degrading Enzyme in Alzheimer's Disease: A Meta-analysis. Current Alzheimer research. 2018;15(7):610-617.
50. Momeni P, Ferrari R. Genetic and blood biomarkers of Alzheimer's disease. The Open Nuclear Medicine Journal. 2010;2:12-24.
51. Seripa D, et al. Role of CLU, PICALM, and TNK1 Genotypes in Aging With and Without Alzheimer's Disease. Molecular neurobiology. 2017; 55(5):4333-4344.
52. Ooi EL, et al. Novel antiviral host factor, TNK1, regulates IFN signaling through serine phosphorylation of STAT1. Proceedings of the National Academy of Sciences. 2014;111(5): 1909-1914.
53. Belbin O, et al. Investigation of 15 of the top candidate genes for late-onset Alzheimer's disease. Human genetics. 2011;129(3):273-282.
54. Chin-chan M, et al. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Frontiers in cellular neuroscience. 2015;9:124.
55. Yegambaram M, et al. Role of environmental contaminants in the etiology of Alzheimer's disease: a review. Current Alzheimer Research. 2015; 12(2):116-146.

56. Durazzo TC, et al. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. Alzheimer's & Dementia. 2014;10(3):S122-S145.
57. Langballe EM, et al. Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway. European journal of epidemiology. 2015; 30(9):1049-1056.
58. Ferreira N, et al. Associations between cognitively stimulating leisure activities, cognitive function and age-related cognitive decline. International journal of geriatric psychiatry. 2015; 30(4):422-430.
59. Winchester J, et al. Walking stabilizes cognitive functioning in Alzheimer's disease (AD) across one year. Archives of gerontology and geriatrics. 2013;56(1):96-103.

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