Genetic Risk Factors for Alzheimer's Disease

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Abstract: Amyloid-Beta plaques and neurofibrillary tangles are the main causes of Alzheimer's disease (AD), a brain condition that results in memory loss and cognitive impairment. Both environmental and genetic factors contribute to it. While the APOE ε4 gene increases the risk of late-onset AD, rare mutations in PSEN1, PSEN2, and APP cause early-onset AD. Other genes, including TREM2, CLU, and PICALM, have been linked to AD by genome-wide association studies (GWAS). Genetic risk is assessed using Polygenic Risk Scores (PRS). However, environmental and lifestyle variables also play a significant role in the development of illness.

1 INTRODUCTION

Alzheimer's disease (AD) represents a significant neurodegenerative condition, recognized as the predominant cause of dementia globally. Neurodegenerative diseases present a big problem for modern medicine and are rising as a more significant health problem around the world. Memory, cognitive processes, and the ability to do daily tasks worsen over time, significantly affecting how people act. Over time, Alzheimer's disease affects people to lose their sense of who they are and greatly increases their independence. This dependence causes much pain for people involved, including the individual in question who has the disease, their family and workers. Alzheimer's disease is the most prevalent type of dementia globally, and its origins are linked to complex factors (Malik, Nasir, 2021). The prevalence of Alzheimer's disease rapidly increases largely due to the aging global population of today. This trend poses a major challenge for healthcare services and society overall. Even with many studies conducted, the precise origins of Alzheimer's disease are still not fully understood (Fu, Mago, Schiff, Krysowaty, 2024).

1.1 Overview of Alzheimer's Disease

The progressive degradation of brain neurons is the hallmark of Alzheimer's disease (AD), which is essentially a neurodegenerative illness. The death of neurons harms brain communication networks, which leads to several cognitive and functional problems. AD is caused by two main types of abnormal protein buildups: amyloid plaques and neurofibrillary tangles. The clinical signs of AD show up slowly at first and get worse over time. Memory problems are often the first and most obvious signs, especially when remembering new information. This could be linked to issues with executive processes like making plans, solving problems, and making choices. As the disease worsens, more and more areas of cognition are affected. These include language (having trouble remembering words and understanding what people are saying), visual-spatial skills (being disoriented and having trouble navigating space), and mental symptoms (e.g. agitation, depression, anxiety, hallucinations) and behavioral. The severity of these symptoms makes it very hard for a person to do daily tasks, making them more dependent on others for help. In the end, the disease causes people to lose their independence, become severely disabled, and, in many cases, die. The disease's misleading symptoms often delay identification, making it harder to start treatment at the right time when it would be most helpful (Sottejeau, Bretteville, Cantrelle, 2015).

1.2 Importance of Genetic Risk Factors

Research has revealed both uncommon and prevalent genetic variables linked to Alzheimer's disease (AD). Human genes contain mutations such as PSEN1, PSEN2, and APP, which are associated with familial early-stage versions of the disease. Conversely, prevalent genetic variants, especially the APOE ε4 allele, are strongly associated with an elevated risk of

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late-onset Alzheimer's disease (AD), the most frequent variant (Santos, Ferreira, 2020). Recent genetic research has identified numerous more genes, including TREM2, CLU, and PICALM, that contribute to the likelihood of acquiring Alzheimer's disease (AD) and offer significant insights into the condition's course. However, environmental, lifestyle and genetics are not the only explanations that are associated with the disease. There are genetic research studies, including large-scale studies and family-based approaches, that have deepened the understanding of how AD is inherited over time. A notable finding can be summarized: employing polygenic risk scores (PRS), which integrate data from various genetic variants, aids in assessing an individual's overall genetic risk for AD. This review studies AD's molecular and genetic field which shows key genetic risk factors and discusses how genes and the environment interact to influence the disease. It also examines the potential of PRS in predicting risk and guiding prevention efforts so the medical field can have access to better diagnostics, targeted treatments, and strategies to prevent or delay of AD (Chouraki, Seshari, 2018).

1.3 Epidemiology of Alzheimer's Disease

The epidemiological data on AD shows a troubling case. Alzheimer's disease leads to brain damage, which is the primary reason for dementia, making up 60–80% of all cases. As people age, this issue occurs more frequently, presenting a significant challenge for the global aging population. Once a person reaches 65 years of age, the likelihood of developing Alzheimer's disease tends to increase twofold approximately every five years. Alzheimer's disease that begins before the age of 65 is uncommon, but it is possible. Many individuals around the globe are presently impacted by Alzheimer's, and this figure is anticipated to increase significantly in the coming decades. The epidemiological data on AD indicates a troubling scenario. Alzheimer's disease is the primary cause of brain damage leading to dementia, representing 60–80% of all cases. As people age, this occurrence becomes much more frequent, presenting a significant issue for the global population that is aging. Once a person reaches 65 years of age, the likelihood of developing Alzheimer's disease typically increases twofold every five years. Alzheimer's disease that begins before the age of 65 is uncommon, but it is possible. Many individuals around the globe are presently impacted by Alzheimer's, and this figure is anticipated to increase significantly in the coming decades. The rising number of cases is a big problem for healthcare systems, which need to spend a lot of money on testing tools, specialized care facilities, and programs to help caregivers. Alzheimer's disease has also a big impact on the economy. It has direct costs like hospital stays, medications, and doctor visits. It also has secondary costs like lost work time and the value of unpaid caregiving by family members. Moreover, the disease affects some groups more than others. Different amounts of risk are caused by things like genetics, race, ethnicity, socioeconomic status, and way of life. Understanding these differences is important for coming up with targeted prevention and response strategies that meet the specific needs of different groups. Epidemiological research offers important information on a number of risk factors. Age, a family history of the illness, certain genetic characteristics, heart disease (including diabetes, high blood pressure, and high cholesterol), inadequate exercise, poor nutrition, and brain traumas are some of these (MD Medicine).

2 MECHANISMS

2.1 Pathophysiology of Alzheimer's Disease

A combination of mutations leads to Alzheimer's disease, which is inherited within families and involves shared risk variants. Amyloid-beta plaques and neurofibrillary tangles are key signs of Alzheimer's disease (AD). Amyloid-beta plaques are deposits formed by misfolded amyloid-beta peptides, while neurofibrillary tangles consist of deposits of hyperphosphorylated tau protein in neurons. This issue leads to an increase in neurodegeneration, synaptic dysfunction, and cognitive loss. Changes in the APP, PSEN1, and PSEN2 genes are the main cause of early-onset familial Alzheimer's disease (EOFAD), since they have a direct impact on the synthesis and accumulation of amyloid-beta. However, APOE-ε4 is the most important genetic risk factor for late-onset Alzheimer's disease (LOAD), which is more common and impacted by a number of genetic variables. Two helpful techniques in Alzheimer's research include familial linkage analysis and genome-wide association studies (GWAS) (Zhou, Yang, Wu, 2023).

2.1.1 Amyloid-Beta Plaque

The amyloid-beta (Aβ) protein, which is present outside of cells, builds up to form amyloid plaques. Amyloid precursor protein (APP), a bigger protein, is the source of the smaller protein known as Aβ. Amyloid precursor protein (APP) processing is disrupted in Alzheimer's disease, which causes amyloid-beta (Aβ) to accumulate in the brain and eventually form plaques. These plaques obstruct neuronal transmission, which causes inflammation and, eventually, the failure and death of the neurons. When these plaques build up, they usually start in memory-related parts of the brain, such the hippocampus, and then move to other parts of the brain, eventually affecting the whole brain. (DeFelipe, Furcila, 2018).

2.1.2 Neurofibrillary Tangles

Neurofibrillary tangles are considered an alternative main cause of disease. They are found inside neurons and mostly contain the protein tau. Tau keeps microtubules stable in a healthy brain. Microtubules are important for moving nutrients and other important things inside neurons. In Alzheimer's disease, tau changes strangely by breaking away from microtubules and forming clumps. These tangles block the transport route within neurons which leads to neuronal dysfunction and, eventually, cell death. There is a clear pattern to how knots form. They start in the entorhinal cortex, that is closely connected to the hippocampus and then spread to other brain parts. The aggravation shows how cognitive decline impacts over time (Medeiros, Vargas, 2011).

2.2 Genetic Foundations

Alzheimer's disease (AD) is also affected by a combination of genetic and environmental aspects. Most Alzheimer's cases come from genetic factors that influence an individual's likelihood of developing the disease as well as the advancement of its symptoms. Studies have revealed that various genetic components linked to AD, such as hereditary patterns and particular genes, increase vulnerability to developing the disease (National Institute on Aging).

2.2.1 Heredity and Family History

Having a family history of Alzheimer's disease (AD) is a significant risk factor for the illness. According to research, those with a first-degree relative who has Alzheimer's disease are two to three times more likely to have the illness themselves than people without a family history. When more family members are involved, the chance increases. Early-onset familial Alzheimer's disease (EOFAD) and late-onset sporadic Alzheimer's disease (LOAD) are the two primary forms of Alzheimer's disease based on how they are inherited. Less than 5% of all AD cases are EOFAD, which is inherited in an autosomal dominant fashion, which means that only one parent possessing the gene may pass on the characteristic. Usually, a diagnosis is made before the age of 65. The majority of AD cases, on the other hand, are caused by LOAD, which has a more complex genetic profile that includes many risk genes as well as the interaction of environmental and genetic variables. (California University).

2.2.2 Genetic Susceptibility Genes

Genetics play a significant role in determining an individual's chances of developing Alzheimer's disease (AD). Recent studies have found additional important genetic factors, such as CLU, BIN1, SORL1, and ABCA7. These genes play a role in different biological processes that help in the development of the disease, including amyloid-beta metabolism, synaptic function, and the inflammatory response. The APOE ε4 allele is an important genetic factor linked to late-onset Alzheimer's disease. People with one or more copies of this allele have a much higher chance of getting the disease. However, the relationship between this gene and the increase of Alzheimer is still unclear. Other genes appear to be linked to Alzheimer's. For instance, the CLU gene plays a role in removing amyloid-beta from the brain, while the BIN1 gene is associated with tau tangles. These genes illustrate the complexity of the genetics involved in Alzheimer’s disease. (Sims, Lee, 2014). Additionally, genes and outside factors, like lifestyle and environment, make it more complicated to understand why some people are at higher risk for Alzheimer’s. Researchers continue to study this disease to find more genes that might increase the risk and to see how these genes work with environmental factors (Huang, Zhang, 2021).

2.3 Genetic Research Methods

Recent progress in genetic research has improved the capacity to pinpoint genetic risk factors linked to Alzheimer's Disease (AD). Genome-Wide Association Studies (GWAS) and Family Linkage Analysis are important techniques that help advance research on Alzheimer's disease.

2.3.1 Genome-Wide Association Studies (GWAS)

Among these, GWAS shows itself as a powerful technique for finding genetic variations linked to complex diseases like AD (Zhang, Li, 2006). This method involves examining the genomes of many individuals, comparing those diagnosed with AD to a healthy group, and identifying specific genetic variations called single nucleotide polymorphisms (SNPs) that are more prevalent in individuals with the disease. However, even though GWAS has provided significant insights, it does have limitations. GWAS approach primarily recognizes common genetic variants, which may not have significant individual effects, and often misses rare mutations as well as important gene-environment relations. Furthermore, the results of GWAS studies need functional validation to prove their causal roles in the development of AD (Jansen, Savage, 2020). As of now, GWAS has found more than 50 genetic sites linked to Alzheimer's disease. This research has discovered key signs, including APOE, CLU, BIN1, SORL1, and ABCA7 which represent important roles in amyloid-beta metabolism, immune response, and tau pathology (Kunkle, Grenier-Boley, 2019). Moreover, the approach called Polygenic Risk Scores (PRS) enables researchers to assess a person's total genetic risk for Alzheimer's by considering various genetic risk factors (Rmanan, Kim, Holohan, 2012). Moreover, analysis that use data from GWAS show significant biological processes related to Alzheimer's disease. The processes include endosomal transport, inflammation, and lipid metabolism, which are crucial for understanding the mechanisms to the disease (Dai, Li, Xue, 2022).

2.3.2 Family Linkage Analysis

Family linkage analysis is a method used to find genetic factors related to Alzheimer's disease (AD), particularly in families where several members are impacted. This method consists of examining families with several individuals diagnosed with AD to be able to trace the heritage of specific genetic characteristics in the genes that has been passed down. By taking this approach, researchers are able to identify particular areas of the genome that might board genes associated with the disease (O'Brien, Wong, 2017). When researching early-onset Alzheimer's disease (EOFAD), a rare genetic type of the disease that usually appears before the age of 65, this method works particularly well. Mutations in certain genes, such as APP, PSEN1, and PSEN2, which contribute to the production and accumulation of amyloid-beta, a significant protein connected to the disease, are commonly linked to EOFAD (Jack, Holtzman, 2017). Family linkage analysis reveals genetic markers that might not be evident in irregular instances, in contrast to the more frequently studied late-onset Alzheimer's disease (LOAD). Researchers have discovered several important risk genes that affect amyloid-beta metabolism, tau pathology, and synaptic function by identifying specific genetic regions through linkage analysis (Alzheimer's Association, 2023).

3 IMPACT AND RISK DISCUSSION

3.1 Major Genetic Risk Genes

Alzheimer's disease is a condition influenced by both genetic and environmental. APOE ε4 allele is a key genetic risk factor, also known as mutations in the PSEN1 and PSEN2 genes. These factors play a significant role in the possibility of developing the disease, which could affect the process such as the production and clearance of amyloid-beta, neuronal health, and cognitive decline. Although genetic testing can indicate people who may have a higher risk for Alzheimer's, the interaction between genetic factors and environmental influences complicates the ability to predict and prevent the disease (Mayo Clinic)

3.1.1 APOE Gene and Its Isoforms

The APOE (Apolipoprotein E) gene is the most significant genetic risk factor for Alzheimer's disease (AD), especially the most common kind, late-onset Alzheimer's. APOE helps transport lipids like cholesterol to brain cells and is crucial for the removal of amyloid-beta, a protein that may build up and form plaques in the brain (National Institute of Aging, 2021). The three primary variations of APOE are ε2, ε3, and ε4. Because it raises the risk of Alzheimer's, the ε4 variation is one to watch out for. Individuals who have one copy of the ε4 mutation are at high risk, but those who have two copies (homozygous for ε4) are much more likely to get the disease. More amyloid plaques, which can impair brain function and cause cell death, are associated with APOE ε4. However, the precise mechanism by which the APOE ε4 variation increases the risk of Alzheimer's disease is still being investigated. This variation is believed to affect the brain's ability to

eliminate amyloid-beta more difficult. It may also contribute to inflammatory reactions in the brain, which could exacerbate the illness. Furthermore, Alzheimer's disease is not always the result of harboring the APOE ε4 variation. Numerous other genetic and environmental variables also have a substantial impact on the disease's progression (Miglio, Vanzulli, 2021). The APOE gene's ε2 variant may provide some protection against Alzheimer's disease by lowering the risk of the condition. Nonetheless, the ε3 variant is the most common and is thought to be neutral (Gong, Zhang, Zeng, 2020).

3.1.2 PSEN1 and PSEN2 Genes

Other mutations that specifically affect early-onset Alzheimer's disease (EOFAD) exist in addition to the APOE gene. Usually affecting those under 65, the mutations constitute a rare form of the disease. The PSEN1 (Presenilin 1) and PSEN2 (Presenilin 2) genes are the primary sites of these alterations. The synthesis of proteins essential for breaking down amyloid precursor protein (APP) into smaller fragments like amyloid-beta depends on the PSEN1 and PSEN2 genes (Sanchez, Kaciroti, 2017). This mechanism breaks down when PSEN1 and PSEN2 mutations occur, which ultimately results in an excess of amyloid-beta, particularly the dangerous type known as Aβ42. This poisonous form has the ability to aggregate and create plaques, which obstruct brain cell-to-cell contact and result in cell death. Alzheimer's disease-related cognitive impairment can be explained by this process (Bertram, Tanzi, 2016). The most frequent cause of EOFAD is mutations in the PSEN1 gene, which frequently exhibit a "autosomal dominant inheritance pattern". In other words, they can develop the disease simply by inheriting one mutated copy from a parent. Mutations in the PSEN2 gene can also cause EOFAD, but they are much less common and don’t always lead to the disease in everyone who carries them (Alzheimer’s Research UK, 2024). The role of the PSEN1 and PSEN2 mutations shows how important amyloid-beta production is for the development of Alzheimer’s. While there is a strong link between PSEN1 mutations and early-onset Alzheimer's, having these mutations alone does not mean a person will develop the disease, as other genetic, environmental, and lifestyle factors also affect whether the disease will occur (Alzheimer’s gov, 2022).

3.2 Secondary Genetic Risk Genes

Other genetic variables can raise an individual's risk of getting Alzheimer's disease (AD), in addition to important genetic factors such as alterations in the APOE, PSEN1, and PSEN2 genes. These secondary genes might not have as strong an effect as the main risk genes, but they still play an important role in understanding how Alzheimer's works. Other key factor genes include TREM2, CLU, PICALM, and others identified in studies like Genome-Wide Association Studies (GWAS) (Gatz, Reynolds, 2006).

3.2.1 TREM2 Gene

Due to its association with Alzheimer's disease, particularly the late-onset variant (LOAD), the TREM2 (Triggering Receptor Expressed on Myeloid Cells 2) gene has gained significant attention in recent studies. TREM2 is essential for the brain's immunological response and is mostly located in microglia, the immune cells that make up the brain. It has been demonstrated that some mutations in the TREM2 gene, particularly the R47H variant, increase the risk of Alzheimer's disease. TREM2 aids in the removal of toxic compounds such as amyloid-beta plaques by brain cells known as microglia. This cleansing mechanism malfunctions when TREM2 mutations occur, resulting in an accumulation of amyloid-beta and increased inflammation, both of which can worsen brain injury. This highlights the role inflammation plays in Alzheimer's disease development (Guerreiro, Wojtas, 2013). TREM2 mutations are extremely uncommon and account for a very small percentage of Alzheimer's cases, despite the fact that the R47H mutation significantly raises the chance of developing Alzheimer's (Wang, Cella, 2015).

3.2.2 CLU, PICALM, and Other Genes

Another significant genetic risk factor for Alzheimer's disease is the Clusterin (CLU) gene. It generates a protein that aids in the brain's amyloid-beta removal. Changes in the CLU gene can lead to problems with clearing amyloid-beta that causes it to build up. CLU is thought to help with the amyloid-beta clumping and manage inflammation and cell survival. Studies indicate that individuals with specific variants of the CLU gene face an increased chance of developing Alzheimer's that makes it a

significant risk factor in the genetic research surrounding the disease (Zhao, Wu, Li, 2019).

Helping to eliminate amyloid-beta from the brain is one of clusterin's primary functions. The breakdown of another protein, amyloid precursor protein (APP), results in the production of amyloid-beta. Amyloid-beta accumulates and creates plaques that damage brain cells if it is not efficiently removed. In order to prevent amyloid-beta from becoming poisonous, clusterin attaches to it and facilitates its removal from the brain. If CLU doesn't work properly, it can lead to plaque buildup, a common feature of Alzheimer's disease. Some studies also suggest that clusterin may affect how quickly amyloid-beta forms into plaques (Wojtas, Kang, 2017).

Studies have revealed a strong correlation between late-onset Alzheimer's disease and a particular variant of the CLU gene (rs11136000). The T form of this gene variant reduces inflammation in the brain and improves amyloid-beta reduction, which lowers the risk for AD. Conversely, the variant's C form is linked to an increased risk of AD, presumably as a result of its decreased ability to remove amyloid-beta. When paired with other genetic and environmental factors, these genetic variants can raise the risk of Alzheimer's disease, but they do not alone cause it (Ling, Simpson, 2012).

CLU and another gene called APOE play similar roles. Both genes help manage fat transport and cholesterol in the brain, which are considered vital for healthy brain function and communication between nerve cells. Clusterin works with APOE to transport fat by helping to keep brain cells healthy. Problems with fat transport can impact amyloid-beta processing and make brain cells more vulnerable to damage. For people with the APOE ε4 variant, certain CLU variations can increase or decrease their risk for AD by impacting how amyloid beta is handled (Montagne, Nation, 2020).

The PICALM (Phosphatidylinositol Binding Clathrin Assembly Protein) gene makes a protein that is essential for a process that helps cells take up amyloid-beta and perform other functions. PICALM has been linked to how effectively amyloid beta is cleared from the brain, and certain variants of this gene also increase the risk of Alzheimer's. Studies suggest that PICALM may affect tau pathology, which is related to the development of amyloid-beta. Additionally, some versions of PICALM may play a role in how much amyloid-beta builds up in the brain, which suggests it could be important in the early stages of Alzheimer's. However, like TREM2, the risk from PICALM variants isn't as strong as that from primary risk genes like APOE (Zhao, Wang, Zhou, 2022)

3.3 Gene-Environment Interaction

3.3.1 Interaction between Environmental Factors and Genetic Susceptibility

Stress, physical exercise, exposure to toxic substances, and our diet can all alter how our genes affect our risk of Alzheimer's. Due to differences in their genes and the ways in which they are expressed, various persons are at different genetic risk. For instance, one of the main genetic risk factors for late-onset Alzheimer's disease is the APOE ε4 allele. But not everyone who carries this gene will develop the illness, demonstrating the importance of environmental factors as well. Research has shown that lifestyle choices can either make the effects of APOE ε4 worse or better. For instance, people with the APOE ε4 gene who exercise regularly, eat healthily, and have active social lives might have a lower risk of cognitive decline compared to those who are inactive. Additionally, exposure to air pollution and heavy metals has been linked to a higher risk of Alzheimer's, especially for those who are already at genetic risk (Lourida, Hannon, 2021).

3.3.2 Influence of Lifestyle

A person's lifestyle (what they eat, how much they move, whether they smoke or drink alcohol, and how engaged their mind is) plays a significant role in how genetic risks for Alzheimer's can impact them. One well-known example is the Mediterranean diet, a way of eating rich in fruits, vegetables, healthy fats, and whole grains. This diet has been shown to help protect against memory decline and Alzheimer's, especially in people who may be genetically at risk. The foods in this diet can fight damage in the brain that leads to Alzheimer's (Shannon, Stephan, Granic, 2023). Even for people who are genetically predisposed to Alzheimer's, maintaining an active lifestyle can lower the risk of the disease. Exercise helps support new brain cell growth and lowers harmful substances in the brain, which provides protection against the disease. Also, keeping the mind active through learning and social interactions can lower the risk of dementia which indicates that mental challenges may help counterbalance genetic risks for Alzheimer's. [41] Epigenetic changes, which can affect how genes behave without changing the

DNA itself, are another way lifestyle factors can influence Alzheimer's risk. Changes in gene expression brought on by factors like nutrition, stress, and exposure to toxins may be inherited by offspring. For example, long-term stress and lack of good sleep have been linked to changes in genes that are involved in brain health, which could speed up Alzheimer's development in those who are already genetically vulnerable (Rodriguez, Delgado, 2023).

3.4 Polygenic Risk Scores (PRS)

Polygenic risk scores (PRS) are a way to measure how likely someone is to develop Alzheimer's disease (AD) based on their genes. Instead of looking at just one gene, like the APOE ε4 allele, PRS considers many different genetic variations found throughout the genome. This method gives a broader view of a person's genetic risk and helps sort individuals into different risk levels for Alzheimer's (Tan, Bonham, 2023).

3.4.1 Calculation and Significance of PRS

PRS is calculated by adding up the effects of different risk genes in a person's DNA.

$$PRS = \sum_{i=1}^{n} (\beta_i \times X_i) \quad (1)$$

In this formula:

- β_i shows how much each risk gene affects the chance of getting Alzheimer's.
- X_i shows how many copies of that risk gene a person has (either 0, 1, or 2).

PRS is mainly useful because it gives a personalized estimate of a person's risk for Alzheimer's disease. Research shows that people with higher PRS scores are more likely to develop Alzheimer's, even if they don't have the well-known risk gene (APOE ε4). PRS can help identify at-risk individuals early, which allows them to make lifestyle changes, get preventative care, or be treated more attentively.

3.4.2 Application of PRS in Prediction and Prevention

PRC scores look at many different genes because some diseases are not caused by just one gene but by many that each contribute a little bit to a person's risk. PRS merges the effects of these genes to show how likely it is that someone will develop a certain condition. The higher the score, the greater the risk. This information can help doctors and patients make informed decisions about their health (National Human Genome Research Institute)

One of the main uses of PRS is to predict health risks. For example, researchers have discovered genetic markers linked to diseases like Alzheimer's. By calculating a PRS, doctors can identify people who may be at higher risk even before they show any symptoms. This early detection is crucial because it lets individuals and healthcare providers take action early to manage the risk (Lewis, Vassos, 2021).

Specific and personalized prevention methods can be applied after identifying individuals at risk through PRS depending on each individual who has attained AD. This might include lifestyle changes like eating healthier, exercising regularly, or getting more mental stimulation. For instance, someone who is found to have a high genetic risk for heart disease may be encouraged to follow a heart-healthy diet or increase physical activity to reduce their risk. In some cases, people with a high genetic risk of certain cancers may need more frequent medical check-ups or screenings. Healthcare providers can help improve health outcomes by applying prevention methods to the individual's genetic risk (Torkamani, Wineinger, 2022).

4 CONCLUSION

4.1 Summary of Main Findings

Alzheimer's disease (AD) is a complex brain disorder affected by several different factors, including genes, the environment, and lifestyle choices. This paper looked at critical genetic factors that contribute to AD such as APOE ε4 gene and other mutations linked to early-onset familial AD in genes such as PSEN1, PSEN2, and APP. There are also other genetic factors like TREM2, CLU, and PICALM, that offer understandings to how the disease works, especially when it is subject of regarding how the brain clears harmful proteins, manages inflammation, and processes fats. The way genes and the environment like diet, exercise, and exposure to toxins interact makes understanding AD even more challenging. New tools called Polygenic Risk Scores (PRS) can help assess risk more precisely by looking at multiple genetic variations at once. PRS can help in early detection, personalized treatments, and targeted prevention strategies. It can suggest interventions, such as lifestyle adjustments and preventive strategies, that could help delay the onset and progression of the disease when healthcare providers can effectively identify individuals with a greater genetic inclination.

4.2 Clinical and Public Health Implications

Understanding genetic risk factors for Alzheimer's disease (AD) is necessary for healthcare and public health. Testing for genetic risks in people who are at high risk can help with earlier diagnoses and better treatments. Public health campaigns that encourage brain-healthy habits, like eating the Mediterranean diet, staying physically active, and keeping the mind engaged, can help reduce the number of AD cases in the community. Personalized medicine that considers genetic risk can make prevention and treatment even more effective, which can potentially lead to better results for patients and less impact on society from AD.

4.3 Future Research Directions and Unresolved Questions

Despite advances in genetic research, many questions remain unanswered about Alzheimer's disease (AD). Future studies that explore how genetics and environmental factors work together to affect the risk of developing AD will push the current healthcare knowledge even further as it is important to improve the accuracy of Polygenic Risk Scores (PRS) for different populations, as genetic risks can vary by ethnicity as well. Additionally, by understanding how changes in gene activity, known as epigenetics, give more spotlight to Alzheimer's Disease research, could help develop new treatments. As we gain more insights into the genetics of AD, prevention strategies and innovative treatments become vital when managing this neurodegenerative disease.

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