Risk Factors of Alzheimer's Disease and Their Impact on Diagnosis and Treatment: A Review

Saanvi Bhat

Abstract

Alzheimer's disease is a progressive neurodegenerative disease, and the most common form of dementia. It can be detected through the abnormal accumulation of beta-amyloid and tau proteins in the brain. These proteins contribute to the atrophy of the brain, due to amyloid plaques formed by the amyloid precursor protein (precursor to beta-amyloid proteins) and neurofibrillary tangles formed by tau proteins (National Institute on Aging, 2024). The exact etiology of this disease is still unknown, and there are many factors that contribute to the etiology of Alzheimer's disease, including genetics and comorbidities. There are a few genes implicated in increasing the risk of developing Alzheimer's disease, including early-onset Alzheimer's disease. Additionally, particular variants of these genes can have differing effects on developing the disease itself (National Institute on Aging, 2023). Other comorbidities, such as type 2 diabetes and some cardiovascular diseases, can increase the risk of an individual developing Alzheimer's disease (Santiago & Potoshkin, 2021). Furthermore, there are two different modalities of treatment for this disease–drugs that change its progression or drugs that mitigate its symptoms, and different medications approved within each type (Alzheimer's Association, 2022). Additionally, antidiabetic medications that utilize dysregulated pathways common to Alzheimer's disease and Type 2 diabetes are being investigated as a potential therapy for Alzheimer's disease, however, current data is inconclusive (Michailidis et al., 2022). With an overview of the prominent genetic factors, comorbidities, as well as current treatment options, this paper discusses the implication these findings have on early diagnoses and potential treatments.

Introduction

Alzheimer's disease is a neurological condition that is progressive over time, resulting in cognitive decline (Mayo Clinic, 2023). It is the most common form of dementia such that of the 55 million people in the world with dementia approximately 60-80% have Alzheimer's disease. While Alzheimer's disease was the sixth leading cause of death in the U.S. in 2014, the true number of these deaths is likely higher due to undiagnosed or misdiagnosed cases. Thus, it is estimated that the number of Alzheimer's-related deaths may be around seven times higher than reported, ultimately making it the third leading cause of death amongst older Americans. The reason for this under-reporting stems from the fact that symptoms of Alzheimer's can coincide with other neurodegenerative diseases (Yokoyama et al., 2018).

Alzheimer's disease is caused by an abnormal build-up of two proteins in the brain, beta-amyloid and tau. The beta-amyloid protein is formed from the breakdown of a larger protein called the amyloid precursor protein (APP). In a brain with Alzheimer's disease, abnormal levels of APP clump together to form neuritic plaques that ultimately disrupt cell function by preventing neurons from synapsing with each other, leading to the death of neuronal cells (Cleveland Clinic, 2022). While healthy brains exhibit nearly the same levels of the beta-amyloid protein as the brains of Alzheimer's disease patients, however, the clear distinction between the two is that

the brains of Alzheimer's disease patients have an abundance of beta-amyloid plaques due to an inability to clear the excess amyloid from the brain (Thorwald et al., 2022).

Normally, neurons are internally supported by microtubules, which guide nutrients and molecules from the body of the cell to the axon and dendrites. Tau molecules bind to microtubules to support and stabilize the microtubules in healthy neurons, but in patients with Alzheimer's disease, abnormal chemical changes can cause tau molecules to detach from their microtubules and stick to other tau molecules. This forms threads of tau molecules that eventually join to form neurofibrillary tangles inside neurons, which block their transport system and interfere with the synaptic communication between neurons (National Institute on Aging, 2024). The brain change in patients with Alzheimer's disease is often attributed to many factors, among which include abnormal levels of tau proteins, beta-amyloid proteins, and several other factors (National Institute on Aging, 2024).

Alzheimer's disease is gradual, with beta-amyloid plaque and tau buildup accumulating for years before symptoms occur. Initially, Alzheimer's disease damages the connections between neurons in the temporal lobe. The first connections begin to decay in the entorhinal cortex, an area that functions as a network hub for memory, navigation and time perception, as well as in the hippocampus, an area responsible for memory and learning, but over time alters other areas, including the parietal lobes, the area of the brain responsible for sensory perception. Eventually, connections among networks of neurons throughout the brain break down, causing the brain to atrophy. This degenerative nature of the disease contributes to the various symptoms, which can be classified with the stage of the disease.

According to the Brain Facts, a primer on the brain and the nervous system, early stage symptoms include greater than expected memory problems, as well as disorientation regarding time and place. Mild stage symptoms can include personality and behavior changes, repeating questions, and taking longer to complete daily tasks. Many people are diagnosed with Alzheimer's disease at this stage. In the moderate stage, symptoms include a difficulty in recognizing friends and family, problems coping with new situations, hallucinations, delusions, paranoia, and impulsive behavior. In the late stage, the patient is reduced to being completely dependent on others for care, as the body begins to shut down. Other symptoms can include weight loss, seizures, difficulty swallowing, and a lack of bowel and bladder control (Yokoyama et al., 2018).

As the early stage phase can prolong for many years before an accurate diagnosis, researchers are investigating biomarkers that can concretely display Alzheimer's disease within a patient. Diagnostic methods can include brain imaging and examining cerebrospinal fluid or blood (Yokoyama et al., 2018). Neuroimaging utilizes mildly radioactive chemical markers that bind to amyloid plaques, showing their location, either with positron emission tomography (PET) scans, single-photon emission computed tomography (SPECT) scans, or magnetic resonance imaging (MRI) scans. However, they cannot reliably be used to identify presymptomatic conditions in patients before the early stage of Alzheimer's disease. Combining imaging and cerebrospinal fluid biomarkers greatly improves the accuracy of diagnosing Alzheimer's disease. The biomarker within cerebrospinal fluid that is related to beta-amyloid proteins is called Aβ42, the 42-unit long peptide form of beta-amyloid that is the most dominant biomarker associated with Alzheimer's. It is inversely proportional to the amount of neuritic plaques within the brain, with lower amounts of Aβ42 indicating higher numbers of neuritic plaques. Other biomarkers use tau proteins, such that high levels of total tau and hyper-phosphorylated tau proteins within cerebrospinal fluid are associated with Alzheimer's disease, due to the formation of

neurofibrillary tangles in a brain with Alzheimer's disease. There are many forms of hyper-phosphorylated tau biomarkers, including P-tau181, P-tau217, and P-tau231, and each perform better in different situations (Gunes et al., 2022).

Other types of biomarkers include electroencephalograms (EEG), which track the electrical impulses generated through neuronal activity through the usage of small electrodes placed atop the scalp. These electrical impulses are displayed as waves. Individuals with Alzheimer's disease generally experience a slowing of electrical activity, displayed as a reduction of higher frequency waves. EEGs are a promising candidate for a biomarker, as the power spectrum, complexity, and synchronization characteristics of EEG waveforms in patients with Alzheimer's distinctly deviate from elderly individuals who have normal brain function (Gunes et al., 2022).

While the cause of Alzheimer's remains unknown, several risk factors have been identified that may contribute to disease onset. This paper will discuss the prominent genetic factors and comorbidities that contribute to the development of Alzheimer's disease, and their implications on early diagnoses and potential treatments of the disease.

Genetic Risk Factors Underlying Alzheimer's Disease

While there are many risk factors implicated in the etiology of Alzheimer's disease. A primary risk factor is the genetic makeup of an individual. In general, a gene is a sequence of nucleotides in the DNA that code for proteins, which directs specific bodily processes and functions (MedlinePlus, 2020). Genes are hereditary, passed onto an individual by one's parents, thus, people have two copies of each gene. Most genes, between people, are the same, however a small number of genes, less than 1% of the approximately 20,000 protein coding genes in the human genome, vary from each other. These differing forms of the same gene with small differences in their nucleotide sequences are called alleles, and they contribute to the unique physical makeup of a person (MedlinePlus, 2020).

One gene implicated in Alzheimer's disease is known as apolipoprotein E (APOE), located on chromosome 19, which encodes a protein that helps carry cholesterol and other types of fat in the bloodstream. Additionally, this gene comes in several different alleles, APOE ε2, APOE ε3, and APOE ε4; that have different implications on the disease itself (National Institute on Aging, 2023). Since each person inherits two APOE alleles, there are six possible combinations that can occur: 2/2, 2/3, 2/4, 3/3, 3/4, and 4/4. One such variant, APOE ε3, is the most common allele, and is believed to have a neutral effect on the disease itself, such that an individual is neither more vulnerable to or protected against the risk of developing Alzheimer's. Another variant, the APOE ε4 allele, increases the risk for Alzheimer's and is associated with an earlier age of disease onset in certain populations, and is present in about 15-25% of people. 2-5% of the population carry two copies of the APOE ε4 allele, and this is associated with a higher risk of Alzheimer's than having one copy. However, while inheriting the APOE ε4 allele increases a person's risk of Alzheimer's, some people with an APOE ε4 allele never develop the disease. Interestingly, the APOE ε2 allele, which is present in 5-10% of people, may provide some protection against the developing Alzheimer's disease. If Alzheimer's occurs in a person with the APOE ε2 allele, it typically develops later in life than it would in someone with the APOE ε4 gene (National Institute on Aging, 2023).

A study conducted by Griswold et al. published in 2021 found that the cells in the brains of patients with European genetic ancestry had almost 40% more APOE ε4OE transcripts than

the samples from individuals with African genetic ancestry. Furthermore, the samples from the European genetic ancestry with higher levels of APOE ε4 also had more of a type of brain cell called A1 reactive astrocytes, thought to be involved in the neuronal degradation processes in Alzheimer's disease. Currently, the mechanism that leads to this difference in APOE ε4 expression is unknown, but scientists speculate that it is caused by DNA methylation or enhancer/repressor activity, two processes that regulate gene expression (Griswold et al., 2021).

Another gene that is considered a risk factor for Alzheimer's disease is amyloid precursor protein (APP), on chromosome 21 (National Institute on Aging, 2023). This particular gene encodes the amyloid beta precursor protein that is found in many tissues and organs, including the brain and the spinal cord. While little is known about the function of APP, researchers speculate that it may bind to other proteins on the surface of cells or help cells attach to one another (MedlinePlus, 2022). The protein also functions to direct the movement of nerve cells during early development, and is cut by enzymes to create peptides, or protein fragments, some of which are released outside the cell. Peptides, on their own, do not have any particular function. When a chain of peptides is folded, they become a protein, like APP, and only then do carry out cellular functions These peptide fragments include soluble amyloid precursor protein (sAPP), and amyloid beta peptides. Individuals with Down Syndrome have a higher risk of developing early-onset Alzheimer's, as they have an extra copy of Chromosome 21. 50% or more of people living with Down syndrome will develop Alzheimer's with symptoms likely presenting in their 50s and 60s.

Other genes that are implicated in Alzheimer's disease include PSEN1 (presenilin 1) and PSEN2 (presenilin 2), on chromosomes 14 and 1, respectively (National Institute on Aging, 2023). The gene PSEN1 encodes a protein called presenilin 1, a subunit of a larger protein complex called gamma-secretase. The primary function of the gamma-secretase complex is to cleave other proteins into smaller peptides through proteolysis (MedlinePlus, 2021). Additionally, presenilin 1 processes APPs and cuts it into smaller peptides, including sAPP and several versions of amyloid-beta peptides. PSEN2 encodes a protein called presenilin 2, which processes proteins that transmit chemical signals from the cell membrane into the nucleus, which activates genes that are important for cell growth and maturation. Like presenilin 1, presenilin 2 processes APP and works with other enzymes to cut it into peptides, forming sAPP and amyloid beta peptide (MedlinePlus, 2008).

A person whose biological parent carries a genetic variant for either APP, PSEN1 or PSEN2 has a 50% chance of inheriting the altered version of the gene, and if that variant is inherited, the child has a very strong possibility of developing Alzheimer's by the age of 65 and in some cases at an earlier age. In total, less than 10% of all people with Alzheimer's disease develop symptoms early, and for those that do, 10-15% of these cases can be attributed to changes in these three genes (National Institute on Aging, 2023).

Comorbidities Associated With Alzheimer's Disease

Individuals with Alzheimer's disease have been reported to have comorbidities that have been implicated in contributing to disease pathology. One such disease is diabetes. Diabetes is a chronic disease where either the pancreas is unable to produce enough insulin, a hormone that regulates the amount of glucose in the bloodstream, or when the body cannot effectively utilize the insulin that it produces (Mayo Clinic, 2024). There are two different types of diabetes, Type I and Type II. Type 1 diabetes is characterized by deficient insulin production and requires daily glucose intake for treatment (Mayo Clinic, 2024). Type 2 diabetes is characterized by

insufficient usage of insulin within the body, leading to hyperglycemia (high blood sugar). While Type 2 diabetes is preventable, and can be further mitigated by conducting regular blood tests, exercise, and reducing obesity, the cause and prevention of Type 1 diabetes remains unknown (Mayo Clinic, 2024). In 2014, 8.5% of adults 18 years or older in the world had diabetes, and by 2019, diabetes was the direct cause of 1.5 million deaths throughout the world. Around 48% of these deaths by diabetes occurred before the age of 70 years, and in lower-middle income countries, the mortality rate from diabetes increased by 13%. More than 95% of people with a diagnosis of diabetes have Type 2 diabetes (WHO, n.d.).

Type 2 diabetes, in particular, is associated with an increased risk of Alzheimer's disease in a variety of populations, with patients displaying accelerated cognitive decline over 10 years of follow up. Additionally, patients who were prediabetic displayed an increased risk for dementia, suggesting that even early alterations in glucose metabolism triggers neurodegeneration. However, despite the numerous linkages between Type 2 diabetes and Alzheimer's, the mechanism connecting the two diseases is yet to be fully understood. Many theories for this said mechanism include impaired glucose metabolism, vascular abnormalities, and impaired insulin signaling. For example, an increased measurement of average blood glucose level is associated with an increase of cognitive decline and dementia in many studies (Santiago & Potoshkin, 2021).

Another comorbidity that is prevalent in Alzheimer's patients is cardiovascular disease, and specifically, strokes and coronary heart disease have been linked to Alzheimer's disease. Lacunar strokes, or silent brain infarcts, are strokes that occur in the deep parts of the brain, and occur when one of the arteries providing blood to the brain's deep structures are blocked. Many studies have shown that these types of strokes increase the risk of cognitive decline and Alzheimer's disease (Santiago & Potoshkin, 2021). Additionally, the presence of lacunar strokes at baseline more than doubled the risk of dementia, and are associated with brain atrophy and an increased risk of cognitive impairment.

Coronary heart disease, the most common type of heart disease, is implicated in the pathology of Alzheimer's. Many studies suggest that coronary heart disease is a risk factor for cognitive impairment and dementia, with atherosclerosis, or the buildup of cholesterol within arteries, as the underlying cause linking these two diseases. Autopsies taken in 1,000 subjects showed that more than 77% of patients of Alzheimer's patients had atherosclerosis in a subset of arteries in the brain, and subjects with severe atherosclerosis in the carotid and femoral arteries displayed a 3-fold increased risk of dementia. Furthermore, this positive association was stronger in subjects with both atherosclerosis and the APOE ε4 genotype (Santiago & Potoshkin, 2021). Elevated serum cholesterol levels and inflammation, two main determinants and factors leading to atherosclerosis, are linked to Alzheimer's disease (Santiago & Potoshkin, 2021).

Current Therapies and Treatments for Alzheimer's Disease:

At the moment, there are two types of treatment for Alzheimer's disease approved by the FDA: drugs that change the progression of the disease or drugs that mitigate symptoms of Alzheimer's (Alzheimer's Association, 2022).

Many of the drugs that change the progression of Alzheimer's work by targeting beta-amyloid plaques in the brain. Most recently, in July of 2024, the FDA approved a drug called donanemab (Kisunsla), which is administered through intravenous therapy every four weeks. This treatment is for patients with early Alzheimer's disease, including those with mild cognitive impairment or mild dementia due to Alzheimer's, caused by elevated levels of

beta-amyloid in the brain. Donanemab was the third of its kind to treat Alzheimer's in this way. The other two drugs include aducanumab (Adulhelm), an anti-amyloid antibody intravenous therapy delivered every four weeks, and lecanemab (Leqembi), an anti-amyloid antibody intravenous therapy delivered every two weeks (Alzheimer's Association, 2022). Aducanumab and lecanemab were approved by the FDA in 2021 and 2023, respectively. In 2024, it was announced that the production of aducanumab would be halted by its manufacturer, Biogen, in order to reprioritize its resources for Alzheimer's disease, and not for safety or efficacy reasons (Alzheimer's Association, 2024).

While clinical trial participants of these anti-amyloid treatments expressed a reduction in cognitive decline, there are also notable side effects, including serious allergic reactions, infusion-related reactions, headaches, and falls. One notable side effect is amyloid-related imaging abnormalities (ARIA), usually a temporary swelling in particular areas of the brain that resolves over time, and in some instances, small spots of bleeding in or on the surface of the brain with the swelling. Though most people with brain swelling do not have symptoms, some symptoms of ARIA include headaches, dizziness, nausea, confusion, and changes in vision (Alzheimer's Association, 2022). Interestingly, individuals who carry the APOE ε4 allele have an increased risk for ARIA. Thus, it is encouraged by the FDA to carry out genetic testing to see whether the patient has the APOE ε4 allele before initiating treatment so that they are aware of the risk of developing ARIA.

Other treatment options for Alzheimer's disease lessen or stabilize symptoms of the disease for a limited time by targeting certain chemical messengers between the nerve cells. For example, cholinesterase inhibitors are drugs that stop the actions of the enzyme acetylcholinesterase, which breaks down the neurotransmitter acetylcholine (Yokoyama et al., 2018). Patients with Alzheimer's disease have low levels of acetylcholine in their brain due to the damage of nerve cells that use acetylcholine, thus these medications rectify this issue. The three cholinesterase inhibitor treatments approved by the FDA are donepezil (Aricept), which is used to treat all stages of the disease, rivastigmine (Exelon), which is used to treat mild-to-moderate stages of Alzheimer's and dementia from Parkinson's disease, and galantamine (Razadyne), which is used to treat mild-to-moderate stages of Alzheimer's. These drugs were approved by the FDA for use as treatments in 1996, 2000, and 2001, respectively, and are generally well-tolerated by the body. However, common side effects include nausea, vomiting, and loss of appetite (Alzheimer's Association, 2022).

Another treatment that targets certain chemical messengers between the nerve cells are NMDA receptor antagonists. Normally, the neurotransmitter glutamate binds to NMDA receptors, allowing calcium to enter the neuron. In Alzheimer's disease, there are elevated levels of glutamate, causing neurons to become overwhelmed with calcium, causing a condition called neuronal excitotoxicity which further damages the neurons (Yokoyama et al., 2018). By regulating the activity of glutamate, these treatments are prescribed to aid with cognitive abilities. One NMDA receptor antagonist called memantine (Namenda) was approved by the FDA in 2003, for treatment of patients with moderate-to-severe Alzheimer's. Common side effects of this treatment are headaches, confusion, and dizziness (Alzheimer's Association, 2022).

Another treatment regimen combines a cholinesterase inhibitor with an NMDA receptor antagonist: in particular, donepezil and memantine (Namzaric), which was approved by the FDA in 2014 to treat moderate-to-severe Alzheimer's disease. Its side effects include nausea, headaches, confusion, and dizziness (Alzheimer's Association, 2022).

While the list of approved treatments to counteract Alzheimer's disease is small, there are many clinical trials underway to find new and better medications. However, there is a high failure rate overall, and many prove ineffective as they do not target the early pathology of Alzheimer's (Yokoyama et al., 2018). This situation may be addressed through online registries, which work to expedite the process of participant recruitment for clinical trials and prioritize patients with earlier stages of disease progression (Yokoyama et al., 2018).

Other novel treatments are based on the idea that diseases with common dysregulated pathways have similar therapeutic targets, for example, Alzheimer's disease and Type 2 diabetes. The antidiabetic medication, metformin, is currently being investigated as a potential therapy for Alzheimer's disease, though current data is limited and inconclusive (Michailidis et al., 2022).

Discussion

Overall, there are many risk factors associated with Alzheimer's disease, ranging from certain genes and their alleles that may pose an increased risk to comorbidities affected by merging biological pathways. Specific allele combinations of the APOE genotype can result in an increased likelihood for developing Alzheimer's disease, but this likelihood varies depending on ethnic populations. The other genes, APP, PSEN1, and PSEN2, are also heavily implicated in the pathology of Alzheimer's as well. Some comorbidities implicated in the etiology of Alzheimer's include Type 2 diabetes and cardiovascular diseases. Many cellular pathways between Type 2 diabetes and Alzheimer's disease intersect with one another, and some genetic factors implicated in developing Alzheimer's also have a hand in the comorbidities associated with the disease itself.

Unfortunately, Alzheimer's disease is one that can only be properly diagnosed post-mortem, due to the specific characteristics, including the accumulation of beta-amyloid plaques and neurofibrillary tangles caused by the clumping of tau proteins. While a multitude of biomarker tests have been developed for earlier diagnoses, a major challenge for implementing these tests is that they are either highly invasive, requiring procedures like lumbar punctures in order to extract the cerebrospinal fluid, or expensive and labor-intensive, making them impractical for regular use within clinics. However, with further development of mildly-invasive or non-invasive procedures, like EEGs, Alzheimer's can potentially be diagnosed within the earlier stages, increasing the effectiveness of treatment. Furthermore, the APOE genotype, PSEN1, and PSEN2, can detect 45-90% of early Alzheimer's disease patients, and changes in gene expression specific to Alzheimer's disease are being noted and explored to create tests that are either minimally or non-invasive to detect Alzheimer's disease in the early stages.

Another observation is that the risk of developing Alzheimer's disease can vary depending on one's ethnic makeup, due to the specific expression or repression of genes in particular ethnic groups, as was seen in the study conducted by Griswold et al. in 2021. However, a large issue is that minority groups have historically been underrepresented within healthcare, resulting in smaller sample sizes to collect data and analyze from, as was the case with that study. This also adds another unknown, as the underrepresented data could lead to the development of treatments that are ineffective for a large number of populations with Alzheimer's disease, due to differences in genetic and epigenetic makeup. Thus, people from all ancestral backgrounds should be encouraged to partake in both clinical and genetic research, in order to study the particular causes of this disease and develop more effective treatments.

The average rate of survival of a patient with Alzheimer's disease after diagnosis is from 4-8 years, though some can live longer, with up to 20 years post-diagnosis due to other factors.

There is so much that remains unknown about the disease, as it cannot be pinpointed to a singular cause, be it a particular gene or a particular comorbidity. Ultimately, additional research needs to be conducted to understand the specific causes and etiology pertaining to this disease, including identifying specific causal biomarkers, such that patients can be identified at earlier stages to mitigate their symptoms. As the neuronal damage from Alzheimer's disease is irreversible, it is imperative that this disease can be diagnosed as early as possible, so treatments can be administered.

References

Alzheimer's Association. (2022). *Navigating Treatment Options*. Alzheimer's Disease and Dementia. https://www.alz.org/alzheimers-dementia/treatments/navigating-treatment-options

Alzheimer's Association. (2024). *Aducanumab Discontinued as an Alzheimer's Treatment*. Alzheimer's Disease and Dementia. https://www.alz.org/alzheimers-dementia/treatments/aducanumab

APP gene: MedlinePlus Genetics. (2022, April 11). Medlineplus.gov. https://medlineplus.gov/genetics/gene/app/

Cleveland Clinic. (2022). *Alzheimer's disease*. Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/9164-alzheimers-disease

Dubois, B., Christine, Burnie, N., Bozeat, S., & Cummings, J. L. (2023). Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants. *Alzheimer's Research & Therapy*, *15*(1). https://doi.org/10.1186/s13195-023-01314-6

Griswold, A. J., Celis, K., Bussies, P. L., Rajabli, F., Whitehead, P. L., Hamilton-Nelson, K. L., Beecham, G. W., Dykxhoorn, D. M., Nuytemans, K., Wang, L., Gardner, O. K., Dorfsman, D. A., Bigio, E. H., Mesulam, M. M., Weintraub, S., Geula, C., Gearing, M., McGrath-Martinez, E., Dalgard, C. L., & Scott, W. K. (2021). Increased *APOE* ε4 expression is associated with the difference in Alzheimer's disease risk from diverse ancestral backgrounds. *Alzheimer's & Dementia*, *17*(7), 1179–1188. https://doi.org/10.1002/alz.12287

Gunes, S., Aizawa, Y., Sugashi, T., Sugimoto, M., & Rodrigues, P. P. (2022). Biomarkers for Alzheimer's Disease in the Current State: A Narrative Review. *International Journal of Molecular Sciences*, *23*(9), 4962. https://doi.org/10.3390/ijms23094962

Lashley, T., Schott, J. M., Weston, P., Murray, C. E., Wellington, H., Keshavan, A., Foti, S. C., Foiani, M., Toombs, J., Rohrer, J. D., Heslegrave, A., & Zetterberg, H. (2018). Molecular biomarkers of Alzheimer's disease: progress and prospects. *Disease Models & Mechanisms*, *11*(5), dmm031781. https://doi.org/10.1242/dmm.031781

Mayo Clinic. (2023, August 30). *Alzheimer's disease - symptoms and causes*. Mayo Clinic; Mayo Foundation for Medical Education and Research (MFMER). https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447

Mayo Clinic. (2024, March 27). *Diabetes*. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/diabetes/symptoms-causes/syc-20371444

MedLine Plus. (2020, September 17). *What is a gene?* Medlineplus.gov; National Library of Medicine. https://medlineplus.gov/genetics/understanding/basics/gene/

Michailidis, M., Tata, D. A., Moraitou, D., Kavvadas, D., Karachrysafi, S., Papamitsou, T., Vareltzis, P., & Papaliagkas, V. (2022). Antidiabetic Drugs in the Treatment of Alzheimer's Disease. *International Journal of Molecular Sciences*, *23*(9), 4641. https://doi.org/10.3390/ijms23094641

National Institute On Aging. (2023, March 1). *Alzheimer's Disease Genetics Fact Sheet*. National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/alzheimers-disease-genetics-fact-sheet

National Institute on Aging. (2024, January 19). *What Happens to the Brain in Alzheimer's Disease?* National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-happens-brain-alzheimers-disease

PSEN1 gene: MedlinePlus Genetics. (2021, October 27). Medlineplus.gov. https://medlineplus.gov/genetics/gene/psen1/

PSEN2 gene: MedlinePlus Genetics. (2008, December 1). Medlineplus.gov. https://medlineplus.gov/genetics/gene/psen2/

Research, C. for D. E. and. (2024). FDA approves treatment for adults with Alzheimer's disease. *FDA*. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease

Santiago, J. A., & Potashkin, J. A. (2021). The Impact of Disease Comorbidities in Alzheimer's Disease. *Frontiers in Aging Neuroscience*, *13*(1), 631770. https://doi.org/10.3389/fnagi.2021.631770

Tang, M.-X. (1998). The APOE-∈4 Allele and the Risk of Alzheimer Disease Among African Americans, Whites, and Hispanics. *JAMA*, *279*(10), 751. https://doi.org/10.1001/jama.279.10.751

Yokohama, C., Roskams, A. J., Jennings, C., Bilsky, E., DiCicco-Bloom, E., Jensen, F., Giordano, J., Morrison, J., Gothard, K., Remole, K., Eliot, L., Farah, M., Sapiurka, M., Shansky, R., Wingate, R., Diaz Brinton, R., Greene, R., Caminiti, R., Schwartz-Bloom, R., & Dunlop, S. (2018). *Brain Facts* (8th ed., pp. 97–100). Society for Neuroscience. https://www.brainfacts.org/-/media/Brainfacts2/BrainFacts-Book/Brain-Facts-PDF-with-links.pdf (Original work published 2012)