Survey of Genetic Risk Factors for Alzheimer's Disease

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ABSTRACT

This paper surveys a number of discovered genetic risk factors for Alzheimer's Disease (AD). AD is a neurodegenerative disease characterized by memory loss and cognitive decline. AD is distinguished by large depositions of amyloid-beta (Aβ) protein, known as plaques, in areas of the brain. No single gene has been identified to cause Alzheimer's, but several risk factors have been identified. Genetic variants associated with the accumulation of Aβ that have been identified as genetic risk factors for AD include APOE-2, APOE-3, APOE-4, APP, PSEN 1, and PSEN 2. This paper discusses these risk factors, their prevalence, how their connection to AD was discovered, and their level of risk.

Introduction

Alzheimer's Disease (AD) is a progressive brain disorder that causes memory loss and a slow decline in cognitive abilities such as problem solving, reasoning, intuition, and speaking (1). An estimated 6+ million Americans are living with AD in 2023 (2). Common observable symptoms of AD include the inability to recognize familiar people or objects, difficulty concentrating, confusion, delusion, disorientation, repetition in speaking, and irritability (3). The main attribute of AD is an abnormal accumulation of the protein amyloid-beta (Aβ) in the brain. Fragments of Aβ clump together to form plaques that disrupt communication between neurons in the brain (4). Another attribute of AD is an abnormal buildup of a second protein called Tau in neurons in the brain. The microtubules (part of the cell cytoskeleton) of neurons are stabilized by Tau. An abnormal buildup of Tau within a neuron in the brain can cause the neuron's cytoskeleton to collapse, damaging its ability to communicate with other neurons. These "tangles" of Tau in neurons throughout the brain impair learning and memory abilities and cause AD (5). AD is divided into two categories, Early Onset and Late Onset. Early Onset AD affects people under the age of 65, and Late Onset AD affects people 65 and older. Late Onset AD is far more prevalent, affecting 6.5 million Americans as of 2023. Early Onset AD is more uncommon, affecting approximately 200,000 Americans in 2023 (2). Risk for AD can be affected by possession of a genetic risk factor. Although overall symptoms of both Early Onset and Late Onset are the same, their genetic risk factors are different (6).

Genetic Variants & Risk Factors

The human genome is the entire set of genetic information, encoded in DNA (Deoxyribonucleic Acid), belonging to a human. The genome is different from person to person, approximately 0.001% of each person's genome is different (7). Each cell in the human body has its own copy of the genome. DNA is divided into genes, which are the basic units of inheritance. Genes provide instructions for making proteins, which perform tasks to regulate the human body. The genome consists of 20,000 to 25,000 genes, and two copies of each gene, known as alleles. One allele of each gene is inherited from each parent by offspring (8).

A genetic variant is a gene that has a permanent change in its DNA sequence (9). A genetic variant may contain one or more mutations. There are two types of genetic variants: germline and somatic. A germline variant is a type of genetic variant occurring in a reproductive cell. Germline variants are hereditary and can be passed down to offspring. Familial AD is caused by an inherited germline variant. A somatic variant is a type of genetic variant occurring in any non-reproductive (somatic) cell. Somatic variants cannot be passed down to offspring. A somatic variant, occurring in a single somatic cell, can only be passed down to the cell's daughter cells when the cell divides during mitosis. Somatic variants only affect the individual that has the variant (10).

A genetic risk factor is a genetic variant that affects an individual's risk for developing a disease or disorder. Genetic risk factors can be either germline or somatic (11). Different genetic risk factors affect risk for Late Onset AD and Early Onset AD. Genetic risk factors APOE-2, APOE-3, and APOE-4 affect risk for Late Onset AD. Genetic risk factors APP, PSEN 1, and PSEN 2 affect risk for Early Onset AD (12). The human genome consists of two copies, or alleles of each gene in the human body. If two copies of a gene are genetic risk factors, the person's risk will be affected more than it would be if only one copy of the gene was a genetic risk factor (11).

Genetic Risk Factors for Alzheimer's Disease (AD)

APOE

The APOE gene, found on chromosome 19, provides instructions for making a protein called Apolipoprotein E (**13**). VLDL (Very Low Density Lipoprotein) and HDL (High Density Lipoprotein) are lipoproteins (half lipid, half proteins) that transport lipids through the bloodstream (14). Apolipoprotein E binds to VLDL and HDL to transport cholesterol through the bloodstream. APOE has an average length of 299 amino acids (15). Three variants of APOE have been classified as genetic risk factors for Late Onset AD. The three genetic variants of APOE are APOE-2, APOE-3, and APOE-4. APOE-2 decreases risk of developing AD, APOE-3 neither increases nor decreases risk, and APOE-4 greatly increases risk (12).

APOE-2 is the most rare variant of the three, carried by approximately 5% of the American population. Having two copies of APOE-2 or one copy of APOE-2 and one copy of APOE-3 can reduce risk up to 40%. APOE-3 is the most common genetic variant of the three, carried by approximately 75% of Americans (16). Approximately 15% of Americans carry at least one copy of APOE-4. More than 50% of AD patients carry at least one copy of APOE-4. One copy of ApoE4 triples or quadruples AD risk. Two copies of APOE4 increases AD risk tenfold (17).

Hippocampal atrophy, a common characteristic of AD, is the shrinking of the hippocampus, the part of the brain responsible for creating new memories. APOE-2 carriers have slower rates of hippocampal atrophy compared to APOE-3 carriers. The slower rate of hippocampal atrophy in APOE-2 carriers is believed to be the reason for their decreased risk of AD (18). Conversely, rates of hippocampal atrophy are higher in APOE-4 carriers, who have increased risk for AD (19).

The Nigerian Paradox is an anomaly relating to APOE-4 incidence and AD susceptibility in Nigerians. Occurrence of the APOE-4 allele is relatively high in Nigerian populations, but AD diagnoses are lower (20). The reason for this paradox is believed to be the Nigerian diet, which consists of mostly whole grains, such as sorghum and millet, and various root crops, such as cassava and yams (21). This traditional diet is low in cholesterol, which plays a role in Aβ regulation (22). The diet's low cholesterol being the reason for low AD rates in Nigeria despite the occurrence of the APOE-4 risk factor is consistent with the role of apolipoprotein E in cholesterol transport (23). The discovery of the Nigerian diet's possible role in neutralizing the effect of the APOE-4 risk factor for AD suggests that "disrupted cholesterol metabolism may increase the risk of developing AD in part due to the effect of cholesterol on brain ApoE expression." (24).

Klotho

The Klotho gene is located on Chromosome 13 and has a length of 1012 amino acids (25). The Klotho gene codes for the protein Klotho (KL), which is an anti-aging protein that protects oxidative stress (25), provides insulin resistance (26), and aids calcium homeostasis (27). The KL-VS variant of the Klotho gene plays a role in AD pathology. Heterozygosity of the KL-VS variant, i.e. carrying one copy but not two, is associated with lower levels of tau accumulation in the brain (28). Scientists are unsure why the presence of only one copy of KL-VS shows a decline in tau in the brain. 25% of Americans are heterozygous for the KL-VS variant (17).

Heterozygosity of the KL-VS variant has also been shown to decrease the AD risk of the APOE-4 variant. In a study done with a set of Northwestern European APOE-4 carriers above age 60, those that also had a single copy of the

KL-VS variant showed little or no AD symptoms, and significantly less Aβ accumulation in their brains (29). "In this ApoE4 carrier group, carrying one copy — but not two — of the klotho variant reduced Alzheimer's risk by 30%," said Michael E. Belloy, one of the researchers who worked on the study (17). Because the KL-VS variant has been shown to neutralize the risk of APOE-4, drug companies are considering leaving heterozygous KL-VS carriers out of their clinical trials on APOE-4 carriers (17).

APP

The APP gene is 639 to 770 amino acids long, located on chromosome 21, and it provides instructions for making amyloid precursor protein (APP) (30). Amyloid precursor protein is a "precursor" protein; after its formation, it is broken down by enzymes into small peptides (smaller proteins) via proteolysis (the breakdown of proteins into peptides). One of the peptides broken down from APP is amyloid beta (Aβ). Large amyloid beta (Aβ) accumulation in the brain is the main indicator of AD (31**)**.

 In APP proteolysis, along with Aβ, the peptides sAPPa, sAPPb, and APP Intracellular Domain (AICD) are also produced (32**)**. One of the functions of the APP Intracellular Domain (AICD) is to regulate transcription (the transfer of genetic information from DNA to mRNA). AICD binds to several genes by acting as a histone, whose proteins have roles in lipid metabolism, signaling, cell cycling, and protein metabolism. Two genes that AICD targets are the genes that code for the proteins neprilysin (NP) and transthyretin (TTR).

One function of NP is to break down peptides of Aβ in the brain. The higher levels of neprilysin in the brain, the smaller the peptides of Aβ, and therefore, fewer Aβ plaques. Studies have shown that naturally, levels of neprilysin decrease during aging, contributing to the agglomeration of Aβ in older people (33**)**. As a transcription regulator, AICD has the ability to regulate neprilysin expression, and therefore affect levels of Aβ in the brain, a key function in the pathology of Alzheimer's Disease (AD) (34).

TTR is another protein that has been shown to reduce levels of Aβ in the brain (35). The Blood-brain barrier (BBB) serves the function of preventing harmful substances in the bloodstream from entering the brain. The BBB consists of efflux transporters, which push harmful substances out, and influx transporters, which allow non-harmful substances to enter. As a person ages, Aβ efflux transporters are decreased in the BBB and Aβ influx transporters are increased, allowing more Aβ to enter the brain (36). Additionally, once Aβ enters the brain through the BBB, it causes damage to the BBB, allowing increased amounts of Aβ as well as other harmful substances to enter the brain (37). Transthyretin (TTR) reduces Aβ disposition in the brain by acting as an Aβ efflux transporter, to push Aβ out of the brain at the BBB (36). As a transcription regulator, the APP Intracellular Domain (AICD) can control the expression of two different proteins- neprilysin (NP) and transthyretin (TTR) that affect Aβ levels in the brain, and therefore the pathology of AD.

There are three different main variants of the APP gene- APP695, APP751, and APP770, named after their number of amino acids. The AICD produced from APP695 has the ability to act as a transcription regulator, affecting levels of neprilysin and transthyretin levels. However, the AICD produced from APP751 and APP770 do not have the ability (38). The main difference between APP695 and APP751 and APP770 is that APP 751 and 770 contain a Kunitz Protease Inhibitor (KPI Domain) (39). The KPI Domain is a protein produced by APP751 and 770 that folds independently from the amyloid precursor protein (APP) and does not get cleaved during APP proteolysis. The KPI Domain serves many functions related to "blood coagulation, fibrinolysis, inflammation, and ion channel blocking" (40). The specific role of the KPI domain in APP751 and 770 is unknown, but it is suggested that the KPI Domain could be the reason for the inactivity of AICD as a transcription regulator in APP751 and 770 compared to the KPI-less APP695. In the KPI-expressed APP751 and 770, studies have shown that more Aβ is produced than the KPI-less APP695. This suggests an increased risk for AD from the APP751 and 770 variants of the APP gene (41).

Down Syndrome is a developmental condition that occurs when an individual has an extra copy of Chromosome 21. People with Down Syndrome have an extra copy of chromosome 21, therefore, an extra copy of the APP gene (42).

Approximately 30% of people with Down Syndrome in their 50s have AD, and the extra copies of the APP gene are believed to be the reason (43).

PSEN 1

The PSEN 1 gene, located on chromosome 14, has a length of 467 amino acids and shares 65% homology (same structure) to its PSEN 2 counterpart (44). The PSEN 1 gene codes for a protein called presenilin 1 (PSEN1). PSEN1 is part of a protein complex (group of proteins with a function) called y-secretase. The function of y-secretase is to proteolyze various proteins, including the amyloid precursor protein (APP). In APP proteolysis, y-secretase (and other enzymes) breaks the amyloid precursor protein into amyloid beta protein (Aβ) and other proteins such as sAPP, AICD, etc.. Presenilin 1 is the catalytic component of y-secretase (45). Mutations in the PSEN 1 gene can destabilize y-secretase-Aβ interactions, resulting in larger Aβ peptides. If Aβ is not proteolyzed into small peptides from APP proteolysis, it is easier and faster for plaques to form, resulting in AD (46). Hundreds of variants of PSEN 1 have been identified, but most of them possess the same property of destabilizing y-secretase-Aβ interactions to increase risk for Early Onset AD. In a study done on genomic data from ACMG-AMP (American College of Medical Genetics and Genomics- American Association of Molecular Pathology), PSEN 1 had the most AD pathogenic/likely pathogenic variants, followed by APP and PSEN 2 (47). There have been many variants of PSEN1, but most affect risk for AD by the same means.

PSEN 2

The PSEN2 gene is located on chromosome 1 and has a length of 448 amino acids (48). The PSEN2 gene codes for a protein called presenilin 2, which shares 65% homology with its counterpart, presenilin 1 (44). PSEN2 is another catalytic component of the y-secretase protein complex, which conducts the proteolysis of amyloid precursor protein (APP) into the amyloid-beta (Aβ) peptide and others (49). Mutations in PSEN2 can inhibit y-secretase-Aβ interactions, similar to mutations in PSEN 1. However, mutations in the PSEN2 gene account for less cases of AD than mutations in the PSEN1 gene (50). Little is known about variants of PSEN2; specific variants have not been widely identified and studied.

Discovery of Genetic Risk Factors

Genome-Wide Association Studies (GWAS) help scientists identify genes associated with diseases. GWAS are conducted by studying the entire genome of large groups with and without a disease to find SNPs (Single Nucleotide Polymorphisms), or single nucleotide changes in genes (51). If a large group with a particular disease has one or more consistent SNPs that are not consistent in groups without the disease, the gene(s) containing the SNP(s) could be classified as genetic risk factors for the disease. However, a large percentage of the group with the disease has to have the same SNP(s) in a large number of studies for the gene to be a genetic risk factor (52).

Heritability is the measure of influence genetics has on the susceptibility of a disease. Heritability is measured as a percentage; high percentages indicate that genetics has a large influence on susceptibility and low percentages indicate that genetics has a low influence on susceptibility. If a disease has low heritability, susceptibility largely depends on environmental factors (53). Late Onset AD has a heritability of 58-79% and Early Onset AD has a heritability of over 90% (54).

Gene functions are discovered by finding the protein that a gene codes for and the function of the protein. The protein that a gene codes for can be found by sequencing DNA and translating it to amino acids or using knockout mice. The function of a protein is found by modeling its structure and finding the proteins it binds to.

Using cDNA (complementary DNA) sequences generated from RNA sequencing or spliced mRNA sequences, which both contain only the protein coding parts of a gene, the composition of a protein (i.e. the amino acids it is made of) can be determined. Translation between nucleotide sequences to amino acids can be done using the mRNA codon table. Blastx is an example of a computer algorithm that takes in FASTA (Fast-All) formatted DNA sequences, translates them to amino acid sequences of proteins, and searches its database for matching identified proteins (55). Another way to find the protein a gene codes for is using knockout mice. Knockout is the process by which an identified gene is knocked out, or removed in a set of mESCs (Mouse Embryonic Stem Cells). Knocking out the gene prevents the production of protein coded in the identified gene. The growth of the knockout mouse is compared with the growth of a wild-type control mouse that has the identified gene. In a large number of tests with many mice, if a protein that is consistent in the wild-type mice but non-existent in the knockout mice, the protein can be tied to the identified gene that was knocked out in the knockout mice (56).

In the case of Apolipoprotein E (APOE), the protein was discovered before it was mapped to its gene on chromosome 19. An unidentified protein was found attached to lipoproteins HDL (High Density Lipoprotein), LDL (Low Density Lipoprotein), and VLDL (Very Low Density Lipoprotein) for transport of triglycerides and other lipids. The unidentified protein was taken in a blood sample and isolated by gel electrophoresis (57). X-ray crystallography was used to identify its amino acid composition and properties. X-ray crystallography is the method of shining x-rays at a crystal to find out its molecular structure. To find the molecular structure of a protein using x-ray crystallography, it must be converted to a protein crystal. X-ray beams are shined through the crystal to find its structure. X-rays are used because the wavelength of an x-ray is approximately the distance between atoms in a crystal. Atoms in the protein crystal cause x-ray beams to diffract into different directions. Analyzing the directions and angles of the diffraction allows scientists to map out the electron density of the atoms in the protein crystal. This and other methods help scientists determine the structure of the protein (58).

Diagnosis of Alzheimer's Disease

Amyloid-PET (Amyloid Positron Emission Tomography) scans are able to show accumulation of amyloid-beta (Aβ) in the brain. Radiopharmaceuticals (radioactive drugs) such as Amyvid (Florbetapir F18) are injected into a patient's bloodstream and bind to Aβ. When the radiopharmaceutical decays, it releases positrons, which explode and emit gamma rays when colliding with electrons in the body. Areas where the PET-scanner traces back high gamma ray emission have high presence of the radiopharmaceutical, and therefore high Aβ () presence. Plaques of Aβ in the brain are the main feature of Alzheimer's Disease (AD). The image produced by the amyloid-PET scan is able to show the presence of Aβ plaques for AD diagnosis (59). Figure 1 shows the comparison between a negative amyloid-PET showing low Aβ deposition (left) and a positive amyloid-PET scan showing high Aβ deposition. However, amyloid-PET scans are expensive and not rarely used for AD diagnosis. Cognitive tests such as the MMSE (Mini Mental State Examination), which are more commonly used for AD diagnosis do not provide the accuracy of the amyloid-PET scan for AD diagnosis. The amyloid-PET scan is a fairly new innovation (early 2000s); the initial discovery of Aβ plaques in the brain as a characteristic of AD (by Alois Alzheimer in 1906) was found in the autopsy of a patient that had died from a severe form of dementia (59). Other than amyloid-PET scanning, the only clear-cut way to diagnose AD is from an autopsy.
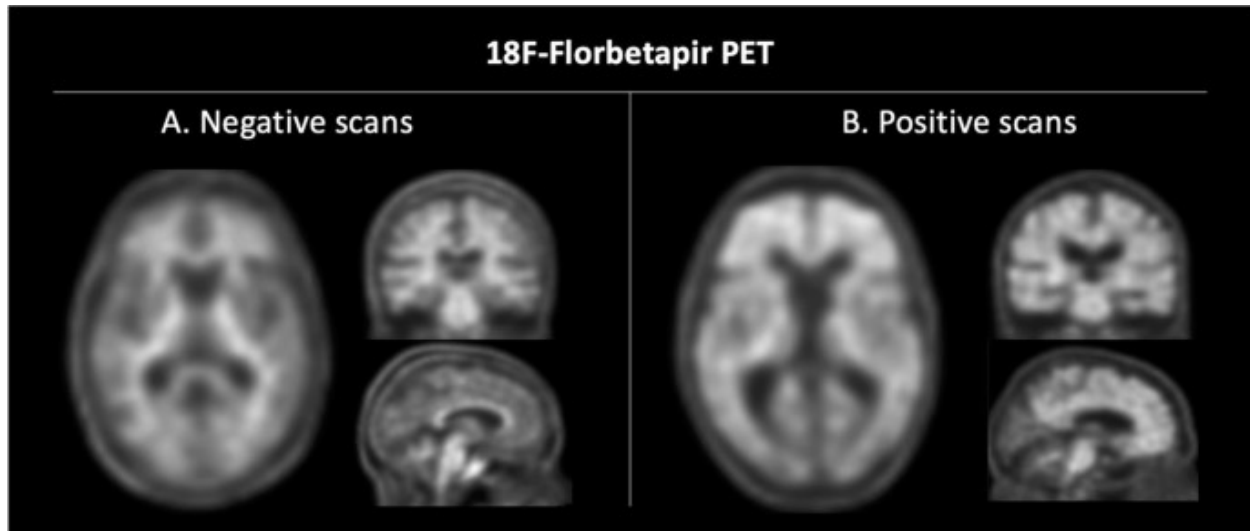
Figure 1. Amyloid-PET Scans. Amyloid-PET Scans showing no Aβ-deposition (left) vs. high Aβ-deposition (right) in the brain. Image Credit- Pietroboni et. al. (60) Image used under Creative Commons Attribution 4.0 International License (61).

Current Research Studies

Genetic Risk Factors

Genome Wide Association Studies (GWAS) are underway for identifying new genetic risk factors for AD, particularly ones of the APP, PSEN 1, and PSEN 2 genes, for which little research has been done so far. Little is known about the correlation between the APOE protein and Aβ protein. However, APOE is the genetic risk factor we know the most about because of its large role in Late Onset AD pathology. Other genetic risk factors, namely the PSEN1 and PSEN2 genes for Early Onset AD are much less common, and less is known about them. Another area of research being done is in the variation of risk between people of different races and ethnicities. It has been found that Alzheimer's rates in the US are higher among African Americans and Hispanics than Caucasians. Conversely, Alzheimer's rates seem to be lower among Native Americans than Caucasians. It is hard to draw conclusions from this research however because of socioeconomic differences (62). It is unclear whether these variations are due to genetics, such as a prevalence of a risk factor in those with a certain ethnicity, or external factors in the environment.

Drug Discovery

Recent drugs such as Aducanumab (Adulhem), Lecanemab (Leqembi), and Donanemab target Aβ to prevent the formation of Aβ plaques that result in cognitive decline (63). Scientists are also trying to develop tau aggregation inhibitors that work to prevent the aggregation of tau in tangles in the brain. Tau aggregation inhibitors are designed to work the same way as drugs such as Clopidogrel, which prevent aggregation of platelets in blood clots (64). Tau-targeting vaccines are also in work; these vaccines are being designed to clear extracellular tau in the brain (65). There is still research to be done on the cause of tau misfolding to form tangles in the brain. Another target of drugs to prevent AD is the enzyme y-secretase, which cleaves the amyloid precursor protein (APP) into amyloid-beta (Aβ) protein. Performance of y-secretase can influence the size of Aβ peptides, and therefore their likelihood of forming plaques, which causes AD. AD is not entirely hereditary- it has a heritability of approximately 75% (54). In addition to genetic risk factors, AD also has a number of external risk factors. These external risk factors include smoking, air pollution, exercise, diet, and levels of cognitive activity (66). Studies have shown that doing cognitive activities, such as games and puzzles can "help prevent AD by preserving brain structures and cognitive functions vulnerable

to AD pathophysiology." (67). Diets, such as the Mediterranean Diet and the adjacent MIND (Mind-DASH Intervention for Neurodegenerative Delay; DASH stands for Dietary Approaches to Stop Hypertension) diet have been shown to decrease risk for AD diagnosis and preserve cognitive abilities in already diagnosed AD patients (68).

Conclusion

This paper surveyed several genetic risk factors for Alzheimer's Disease (AD): APOE, APP, PSEN1, and PSEN2. Possession of one or more copies of these risk factors can affect risk of susceptibility of AD.

Acknowledgements

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