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Genetic factors associated to Alzheimer's Disease

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Abstract

Alzheimer's disease is a neurological condition that gradually impairs memory, self-awareness, and cognitive capacities. It is the most frequent cause of dementia and a major factor in senior patient deaths. It is generally acknowledged that the condition is multifactorial, resulting from intricate interactions between age, genetics, and environment, even though the exact cause is unknown. Early start of the condition can be caused by mutations in the APP, PSEN1, and PSEN2 genes, which can result in an autosomal dominant inheritance pattern. The most prevalent kind is late-onset, in which the APOE ε4 allele is the primary genetic risk factor. TREM2, CLU, and PICALM are among the other genes that raise the risk. The primary molecular pathways are the build-up of beta-amyloid proteins, which result in amyloid plaques, and the hyperphosphorylation of tau, which forms neurofibrillary tangles and causes neuronal death by necrosis, autophagy, and apoptosis. Acetylcholine, glutamate, GABA, and noradrenaline neurotransmission are all impacted, which has an effect on cognition and memory.In conclusion, Alzheimer's disease is a complicated neurological disorder that causes progressive cognitive impairment due to both hereditary and molecular components.

Keywords: Alzheimer's; Neurological; Memory; Cognitive; Genes; APOE ε4

1. Introduction

Alzheimer's disease (AD) is a neurological illness of unknown cause that progressively impairs one's memory, judgment, self-awareness, and cognitive capacities [1].

Alzheimer's disease (AD) is the most common cause of dementia and one of the leading causes of mortality in elderly patients. In 1906, the German psychiatrist and neuropathologist Alois Alzheimer discovered that this symptom begins in adulthood and progressively and irreversibly affects cognitive functions. This symptom has a particular predilection for short-term memory and is related to the accumulation of β-amyloid and hyperphosphorylated tau in the brain [2].

According to the World Health Organization, today more than 55 million people worldwide suffer from dementia, over 60% of whom live in low- and middle-income countries. Every year, there are almost ten million new cases. Alzheimer's disease is the most common form of dementia and can account for between 60% and 70% of cases [3].

The precise cause of AD is unknown, although it is widely accepted that the disease is multifaceted and arises from complex interactions between a number of variables, including age, education, genetics, and environmental factors [4].

An important factor in the etiology and risk of AD is genetics. Due to the extreme heterogeneity of AD, its genetics are complex. In addition to offering fresh perspective on AD pathogenesis, the mapping of genetic data in the disease may

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potentially prove useful for targeted early AD intervention. Linkage analysis, candidate gene analysis, genome-wide association studies (GWAS), and next-generation sequencing (NGS) technology are the primary research methodologies in AD genetics. Furthermore, a number of new risk genetic loci for AD were discovered through the use of cutting-edge like GWAS, which may provide light on the underlying causes of late-onset Alzheimer's disease (LOAD) [4].

Alzheimer's disease is inherited as an autosomal dominant trait in a tiny proportion of cases (<2%). Autosomal dominant Alzheimer's disease is caused by mutations in any one of three. These genes are located on chromosomes 21, 21, and 14, respectively, for the amyloid precursor protein (APP), presenilin 1 (PSEN1), and the closely related presenilin 2 (PSEN2) on chromosome 1. Autosomal dominant illness patients typically present with an early onset [5].

2. Genes

Autosomal dominant Alzheimer's disease (AD) is a rare form of the disease characterized by an early onset between the ages of 30 and 75 and an autosomal dominant inheritance pattern. This means that if one parent has the genetic mutation that causes DAAD, each child has a 50% chance of inheriting it.[6] Evidence from genetics, pathological, and experimental studies has shown that imbalances in the concentration of amyloid-β (Aβ) peptides in the brain cause accumulation and aggregation of Aβ. The toxic Aβ aggregates in the form of soluble Aβ oligomers, intraneuronal Aβ, and amyloid plaques injure synapses and ultimately cause neurodegeneration and dementia. Aβ is composed of 40 or 42 amino acids and is generated through proteolytic cleavage of amyloid precursor protein (APP) [7].

Early-onset familial AD,which usually develops before age of 65 years and accounts for only a small proportion (<1%) of AD cases, is caused primarily by overproduction of Aβ due to mutations in the gene or APP [7].

The majority of AD cases occur later in life (>65 years of age) and are often referred to as late-onset AD (LOAD) [7].

2.1. ApoE

ApoE is a component of plasma lipoproteins that transports lipids between cells in multiple organs and tissues; it is one of several apolipoproteins associated with very low density lipoproteins (VLDL), intermediate density lipoproteins, chylomicron remnants, and certain subclasses of high-density lipoproteins. By acting as a ligand for binding to particular cell surface receptors, such as those in the LDL receptor family, it plays a crucial function in controlling the removal of these lipoproteins from plasma [8].

The majority of ApoE is produced by astrocytes in the central nervous system (CNS).

It is present in non-myelinating Schwann cells and the glia that envelop sensory and motor neurons in the peripheral nervous system (CNP). Macrophages are in charge of producing and secreting ApoE after a peripheral nerve injury. This protein accumulates up extensively in the damaged nerve's extracellular matrix and aids in the regeneration process [8].

There are three polymorphic alleles (ε2, ε3, and ε4) in the human APOE gene, with respective frequencies of 8.4%, 77.9%, and 13.7% [7].

The main genetic determinants of the risk of Alzheimer's disease (AD) are polymorphic APOE alleles: the frequency of the ε4 allele rises to 40% higher in AD patients than in those with the more common ε3 allele, while the ε2 allele lowers the risk [7].

Apo-E isoforms have a variety of roles in controlling brain lipid transport, glucose metabolism, neuronal signaling, neuroinflammation, and mitochondrial function in addition to variably regulating Aβ aggregation and clearance in the brain [7].

The APOE4 variant, known to increase the risk of developing Alzheimer's disease, alters the cholesterol balance in myelin-producing cells and compromises the production of myelin, which is necessary for the correct transmission of nerve impulses [9].

A recent international study led by researchers at the Massachusetts Institute of Technology (MIT) found that APOE4 alters the cholesterol balance in oligodendrocytes, which triggers an intracellular stress situation that leads to a decrease in the production of myelin basic protein and interferes with myelin production. As a final consequence, myelin

production is reduced, which implies a reduction in the thickness of the myelin sheaths covering the nerve extensions [9].

2.2. APOE e4 allele

The strongest known genetic risk factor for Alzheimer's disease (AD) is the APOE e4 allele. People who have two copies of the E4 allele have a significantly higher risk of developing the disease than people who have one or no copies. APOE4 increases the risk of developing AD through a combination of gain of toxic effects and loss of protective functions [10].

APOE e4 is thought to transport lipoproteins less efficiently, which may result in a buildup of betaamyloid and tau in the brain, two abnormal proteins characteristic of AD [10].

APOE e4 can also promote inflammation in the brain, which can damage neurons and help advance AD. Similarly, it can negatively affect the function of synapses, the junctions between neurons, which can cause problems with memory and other cognitive functions [10].

A study using in vivo PET imaging in young adults with the APOE ε4 allele (the main genetic risk factor for Alzheimer's disease) discovered impairments in glucose metabolism in brain regions that are vulnerable to AD, such as the cortex and posterior cingulate [11].

These results, which were published in the "Journal of Alzheimer's Disease," indicated that these metabolic changes may be a precursor to the disease, developing decades before symptoms become manifest [11].

Previous postmortem studies have demonstrated a connection between localized brain mitochondrial dysfunction and similar metabolic reductions in AD. In the posterior cingulate cortex, specifically in the superficial cortical lamina, at-risk ε4 carriers were shown to have reduced mitochondrial cytochrome oxidase activity in contrast to non-carriers. This pattern is comparable to what has been seen in patients with AD [11].

2.2.1. Presenilin 1 gene (PSEN1)

Presenilin 1 gene (PSEN1): this gene encodes a protein involved in the processing of β-amyloid, which is the main component of amyloid plaques in the brains of people with

Alzheimer's disease. Amyloid plaques are extracellular deposits formed by the accumulation of βamyloid and are considered a hallmark of Alzheimer's disease [12].

The most common cause of familial Alzheimer's disease are mutations in the PSEN1 gene, which encodes presenilin-1 (PS1). PS1 serves as the catalytic subunit of the intramembrane protease gammasecretase, which cleaves a variety of type 1 transmembrane proteins, especially amyloid precursor protein (APP) and Notch [13].

Nonsense mutations, small insertions, deletions and genomic deletions are found in the PSEN gene spectrum, especially in PSEN1. The most severe forms of AD with full penetrance are caused by mutations in PSEN1, and the disease can begin to manifest from the age of 25 years, presenting with neurodegenerative dementia due to the loss of essential presenilin functions in the brain when PSEN1 is altered [12, 13].

2.2.2. Presenilin 2 gene (PSEN2)

Presenilin 2 gene (PSEN2): this gene is similar to the PSEN1 gene and encodes a protein used to process amyloid. The likelihood of developing DAAD may increase if mutations occur in the PSEN2 gene [12].

PSEN2 plays a lesser role than PSEN1, but mutant presenilins can enhance Aβ production and contribute to the development of AD [14].

To date, 38 mutations in PSEN2 have been reported. According to cell-based studies, four of these mutations, T122P, N141I, M239I and M239V, increase the number of Aβ peptides.

Variable penetrance and a wide age range of disease onset, from 45 to 88 years, are associated with mutations in PSEN2. Most of these were found at sites in Europe and Africa [14].

2.2.3. Amyloid precursor protein (APP) gene

This gene encodes a protein that cleaves into smaller fragments, including the amyloid beta peptide (β-amyloid). Excessive production of beta-amyloid, which accumulates in the brain and forms plaques, is one of the hallmark pathological features of AD, can be caused by mutations in the APP gene [6].

Carriers of mutations in the APP (amyloid precursor protein) gene usually have a later age of onset of Alzheimer's disease, usually around 50 years of age, with a range from 45 to 60 years [6].

It is important to keep in mind that ADAD is a complex disease and it is likely that genes other than the three mentioned above contribute to its development. In addition, there can be significant variability in the age of onset and severity of the disease even within families with a known genetic mutation. (6) The b-amyloid peptide, which contributes to the obstruction of nerve signals, is produced by the APP gene. Methods have been developed to prevent the production of this peptide, such as inhibition of bsecretase and y- secretase. This will allow for better treatment for Alzheimer's disease [15].

2.2.4. TREM2

Is another gene that has been associated with an increased risk of developing Alzheimer's disease. This gene produces a protein that is involved in the inflammatory response of the brain. Mutations in TREM2 can increase a person's susceptibility to Alzheimer's disease [16].

The susceptibility to late onset Alzheimer's disease is induced by (TREM) 2, which has a probability index similar to that of ApoE 4 allele [17].

TREM1 and TREM2 are the two main members of the TREM family. TREM2 is expressed in microglia, osteoclasts, macrophages and dendritic cells and is associated with DAP12 to perform its signaling function. TREM2 suppresses inflammatory responses by suppressing the production and secretion of microglia-mediated cytokines, as well as participating in the regulation of the phagocytic pathways that are responsible for the removal of neuronal residue. This contrasts with the proinflammatory effects of TREM1 [18].

2.2.5. CLU and PICALM

Are genes that have also been associated with an increased risk of Alzheimer's disease. The proteins produced by these genes are involved in the removal of amyloid beta and tau, two proteins that accumulate in the brains of people with Alzheimer's disease. Mutations in CLU and PICALM can lead to an accumulation of these proteins, which contributes to the development of the disease [19].

Finding a functional dependency between the risk genotypes of PICALM and CLU, two major risk genes for late-onset Alzheimer's disease (LOAD), may help to clarify their roles in the development of LOAD and increase their clinical utility. There is strong molecular evidence suggesting that these genes interact on amyloid-beta deposition [20].

Research on the impact of genetic variations of PICALM and CLU on brain structure and function has been conducted using neuroimaging methods. PICALM risk-allele carriers exhibited thinner entorhinal cortex and reduced hippocampal volume in older participants, including AD patients, as compared to noncarriers [21, 22, 23].

3. Molecular mechanisms by which genes influence alzheimer's disease

3.1. Amyloid plaques and neurofibrillary tangles

Amyloid peptide is a naturally produced polymer and its operation should not be harmful to human health. There are a variety of amyloid varieties, but the one that has no neurotoxic effects is the isoform of 40 amino acids. (A40). The isoform that has harmful effects on the nerves is composed of 42 amino acids (Aβ42). Because of its low polarity and difficulty in dissolving in water, A42 accumulates in areas of the brain, resulting in the formation of senile plates, which have an impact on synaptic spaces because they block the flow of information between neurons [24].

3.2. Chromosome 21 mutation

The chromosome 21 is essential for the synthesis of the amyloid precursor protein, which gives rise to the amphyloid peptide. Senile plaque formation has been shown to depend on mutation in chromosome 21 codon 717 [25].

3.3. Chromosome 17 mutation

The number of fibrillary ovules in the cytoplasm of neurons is directly related to the severity of dementia. They consist of accumulations of mated helicoidal filaments that, compared to normal neurofilaments and microtubules, have distinctive characteristics [25].

Irreversible phosphorylation of the normal tubules of the cell's cytoplasm deforms these tubules, preventing the efficient transport of electrical impulses and nutrients to the brain. [24] A mutation in chromosome 17 responsible for the synthesis of the Tau protein [24] causes changes in the ovules and microtubules due to phosphorylation [24].

3.4. B-amyloid and its precursor protein in neuronal cell death

Beta-amyloid peptide (Aβ) and its derivative, the amyloid precursor protein (APP), play an important role in the development of Alzheimer's disease [26]. Beta-amyloid peptide is the main component of senile plates. This peptide causes cell death through mechanisms such as apoptosis, necrosis and autophagy [26].

3.5. Apoptosis

Cells generally die through the intrinsic pathway (mitochondrial pathway) or the extrinsic route (receptor-death pathway) [27].

Extrinsic pathway: positive regulation of death receptor 6 (DR6, also known as TNFRSF21) promotes apoptosis [28].

Caspase-6-associated axon cutting and caspase-3-related neuronal death have been shown to occur in the brain when a scattered N-terminal of the caspase precursor protein (N-APP) is attached to DR6 [26].

Intrinsic pathway: **:** In patients with Alzheimer's disease, iron and copper have been shown to accumulate near amyloid deposits, as well as the co-occurrence of oxidation of proteins, nucleic acids and lipids; high levels of APP are known to induce oxidative stress [29, 30].

In addition to increasing intracellular calcium levels that cause excitotoxicity, APP accumulation also increases pro-apoptotic molecules and thermal shock proteins [31].

3.6. Necrosis

According to some studies, certain types of necrosis, such as necroptosis, ferroptosis, oxytosis, and pyroptosis can contribute to the development of Alzheimer's disease [32].

A mechanism of necrosis is when there is an increase in cholesterol associated with age. Altered cholesterol levels can affect gamma-secretase and gamma-sekretase activity, interfering with the processing potential of the HAP [33].

Since the processing of APP along the non-amyloidogenic pathway is dampened with aging, neural cells become vulnerable to cellular stress [26].

3.7. Autophagy

With regard to autophagy, research has shown that Beclin 1 protein can be an adaptive protein that improves APP processing or an inducer of autophageal cell death [34].

Beclin 1 deficiency can stop APP processing or divert its distribution to other subcellular compartments, producing more APP fragments, such as intracellular and extracellular Aβ peptides [35].

4. Neurotransmission in alzheimer's disease

The synaptophysine protein of the presynaptic bladder, which is involved in synaptic transmission, decreases by approximately 25% in mild Alzheimer's disease [36].

Several neurotransmitters are affected differently by this neurodegenerative disease, so we will discuss each mechanism as Alzheimer's mediates [36].

4.1.1. Acetylcholine

Neurotoxicity caused by Aβ oligomers has a particular impact on cholinergic synapses and the resulting synaptic loss is the main factor related to cognitive impairment. In addition, an increase in the activity of the enzyme AChE around amyloid plates has been observed [37].

Meynert nuclei have a significant decrease in the transcription of the enzyme AChT, which is the acetylcholine-forming enzyme [38].

4.1.2. Glutamate

The amino acid glutamate is the main exciting CNS neurotransmitter. It interacts with several specific receptors of the neuronal membranes to perform a variety of functions, being one of the mechanisms by which Alzheimer's disease affects the synaptic neurotransmission systems, cognition and memory [39].

The large pyramidal cells of the neocortex and hippocampal formation, which receive and emit glutamatergic impulses, are affected by neuronal loss and neurofibrillary pathology in Alzheimer's disease [39].

Pathologically elevated levels of Aβ have been described as blocking the neuronal absorption of glutamate in the synaptic fissure, which would increase their LCR levels [40].

4.1.3. GABA

The main central nervous system (CNS) inhibitory neurotransmitter is gamma-aminobutyric acid (GABA), which activates the GABA-A and Gaba-B receptors [41].

In a study of how Aβ peptides affect synaptic transmission through the GABA-A receptormediated endocytosis mechanism, it was found that Aβ has the ability to decrease synaptic inhibition by negative regulation of GABA -A receptors [42].

4.1.4. Noradrenaline

A loss of neurons has been observed at the level of the locus ceruleus, a subcortical nucleus of the brain rich in NA-producing neurons (noradrenaline), as well as in the nuclei of the raft, where anatomopathological changes have been seen, such as the presence of neurofibrillary ovules (such as those found in Alzheimer's disease) as a result of the phosphorylation of the tau protein in those regions [43].

The decrease in this neurotransmitter is related to depressive processes and cognitive changes, such as memory and learning deficits. In addition, it has been linked to psychomotor agitation present in Alzheimer's disease [43].

5. Conclusion

Alzheimer's disease (AD) is a neurological disease that affects millions of people worldwide, especially those over the age of 65. AD is characterized by the progressive and irreversible deterioration of cognitive functions, short-term memory. Over the years, research has identified a number of genes implicated in AD, such as APOE, PSEN1, PSEN2 and APP, which play key roles in beta-amyloid (Aβ) metabolism, plaque formation and neurodegeneration. APOE4, in particular, has been revealed as an important genetic risk factor, which increases Aβ accumulation, promotes brain inflammation and affects synaptic function. Other genes such as TREM2, CLU and PICALM are also associated with an increased risk of AD, influencing the clearance of Aβ and tau from the brain. In addition, AD negatively affects several key neurotransmitters, such as acetylcholine, glutamate, GABA and norepinephrine, leading to synaptic dysfunctions and cognitive impairment. This study covers these neurochemical and genetic mechanisms involved in the development of the disease, which is of great use in the medical field for better understanding and to developing effective treatments and early intervention strategies to combat AD.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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