

Analysis of genetic mechanisms, clinical characteristics and pathological changes in familial Alzheimer's disease and sporadic Alzheimer's disease

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Abstract: With the development of modern public health endeavors, Alzheimer's disease (AD) has emerged as an undeniable factor among the aging population. Familial Alzheimer's disease (FAD) and sporadic Alzheimer's disease (SAD) constitute the two primary classifications of Alzheimer's pathology. Through a comparison of their genetic mechanisms, clinical characteristics, and pathological changes, the intention is to unveil the distinctions and similarities between these two types. Research suggests that despite the presence of similar clinical manifestations in both types of Alzheimer's disease, there are significant differences in their genetic backgrounds and pathological features. A comprehensive understanding of the divergences and commonalities between FAD and SAD contributes to a deeper comprehension of the etiological mechanisms and clinical management of AD.

1. Introduction

AD is a prevalent neurodegenerative condition affecting the central nervous system and being the most prevalent manifestation of dementia. According to Dr. Kaj Blennow, AD is a neurodegenerative condition that progresses over time and is defined by the atrophy of the hippocampus and cortex, as well as the loss of synapses and degradation of neurons. The condition is distinguished by a gradual decline in episodic memory, which subsequently progresses to include a range of cognitive domain impairments and mental symptoms. Additionally, it can be accompanied by other non-cognitive manifestations such as Parkinson's syndrome, myoclonus, and epileptic-like seizures. [1] During the advanced phases of the condition, individuals experience a decline in their capacity to carry out routine tasks autonomously, so placing a substantial strain on both families and society at large. The incidence of AD increases with population aging and extended life expectancy. According to statistics, the prevalence of AD among individuals aged 65 and above in China is 3.21% [2]. Given the lack of effective prevention and treatment methods, AD has emerged as a major global public health concern that greatly impacts elderly health and socio-economic development. In-depth research on its pathogenesis and prevention is urgently needed.

In the context of previous research, Alzheimer's disease has been classified into two subtypes: early-onset AD (EOAD, with an age at onset of 65 years or below) and late-onset AD (LOAD, with an age at onset of 65 years or older) [2]. In the field of medical research, the concept related to family history is often categorised into two main

subtypes: familial AD and sporadic AD. This research primarily focuses on the comparison between familial AD and sporadic AD, examining their distinctions and similarities, and contributing to the investigation of their respective onset processes and potential early intervention strategies.

2. Familial Alzheimer's disease and sporadic Alzheimer's disease

The prevalence of Alzheimer's disease is mostly attributed to sporadic instances, which do not follow a Mendelian inheritance pattern. In contrast, autosomal dominant instances constitute less than 1% of the total number of autosomal dominant cases. The sporadic manifestation of AD does not demonstrate familial aggregation, and its features are influenced by intricate genetic and environmental interplays [3]. Familial Alzheimer's disease, from a genetic standpoint, often denotes instances occurring within families that exhibit Mendelian inheritance patterns. An uncommon and highly penetrant mutation affects one of the three major genes, namely Amyloid Precursor Protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2) [4]. These categories do not display any fundamental distinctions in clinical alterations, such as the presence of neurofibrillary tangles and senile plaques [5].

2.1. Genetic Mechanisms

Both Familial Alzheimer's disease (FAD) and sporadic Alzheimer's disease (SAD) have a correlation with

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hereditary variables, but with variations in the exact genes implicated.

The genes PSEN1, PSEN2, and APP are the definitive pathogenic genes associated with EOAD, and their inheritance follows an autosomal dominant pattern. Approximately 80% of cases of early-onset familial Alzheimer's disease have genetic abnormalities in the PSEN1, PSEN2, or APP genes [6]. Over 200 mutation sites associated with disease onset have been identified in the three known FAD-related encoding proteins: APP, PSEN1, and PSEN2 [5]. Furthermore, in a study by Lucía Chávez-Gutiérrez, it was indicated that familial Alzheimer's disease in different regions exhibits genetically distinct mutation sites [7]. The presence of these mutations results in the synthesis of atypical variants of APP and presenilin proteins, both of which play a crucial role in the generation and buildup of amyloid-beta plaques inside the brain (Jia et al., 2020). These plaques are a characteristic feature of AD.

The apolipoprotein E ϵ 4 allele (APOE ϵ 4) is the sole confirmed risk gene for LOAD. Approximately 50-60% of AD patients carry the APOE ϵ 4 allele. The APOE gene plays a crucial function in lipid metabolism and the elimination of A β from the brain, as shown by Jia et al. [8]. Yeh et al. (2016) have identified more genes, including CLU, SORL1, and TREM2, that are correlated with SAD. The genes under consideration have a role in many processes associated with the metabolism of A β , including A β clearance, transport, and absorption by microglia [9]. The frequency of the ϵ 4 allele in AD patients is 2-3 times higher than in cognitively normal individuals. Most studies report increased amyloid deposition and accelerated progression of Alzheimer's disease pathology in the aging brain of individuals expressing the ϵ 4 allele [10].

There are discernible distinctions in the genetic pathways behind FAD and SAD. Familial AD is mostly attributed to genetic mutations in key genes, including APP, PSEN1, and PSEN2 (Petersen RC, 1992). Conversely, Sporadic AD is multifactorial in nature, resulting from a complex interplay of environmental, genetic, and metabolic factors [11].

The etiology of Alzheimer's disease extends beyond mutations in genes like APOE ϵ 4, PSEN1, PSEN2, and APP, as there are numerous other variants significantly contributing to the potentiality for the onset of AD. For instance, rare protein-damaging variants have been identified in genes such as SORL1 (Sortilin-related receptor 1), ABCA7 (ATP-binding cassette A7), and TREM2 (Triggering receptor expressed on myeloid cells 2). The integral protein products expressed by these genes are

crucial for maintaining brain health [12]. Furthermore, there is evidence to suggest that environmental factors also impact FAD. Ambreen Mirza et al. measured elevated levels of aluminum in FAD brain tissues (also present in SAD) and concluded that brain aluminum, under certain circumstances, could contribute to various forms of AD [13].

2.2. Clinical Characteristics

In clinical practice, Alzheimer's disease is often categorized based on age of onset (AAO), with a threshold of 65 years. This classification divides Alzheimer's disease into EOAD (AAO \leq 65 years) and LOAD (AAO > 65 years). EOAD comprises around 5% of all instances of Alzheimer's Disease, and EOFAD accounts for around 61.5% of EOAD cases [14]. The vast majority of instances of AD, accounting for over 95% of cases, exhibit a non-Mendelian pattern of inheritance. These types of dementia are often referred to as LOAD due to their characteristic onset age of 65 years or later. In contrast, familial AD (FAD) constitutes less than 1-5% of AD cases and is caused by mutations in one of three specific genes [14]. The onset age for FAD cases is usually before the age of 65, and these patients are commonly termed as Early-Onset AD [3].

The clinical manifestations and symptoms seen in both FAD and SAD exhibit some parallels, however, they also exhibit distinct distinctions. Regarding typical clinical presentations, both FAD and SAD are characterized by a progressive decline in cognitive functioning, including memory impairment, and a reduction in the ability to perform everyday activities. The cognitive symptoms mentioned are often accompanied by behavioral and psychological symptoms, including sadness, anxiety, agitation, and psychosis [15]. According to Sweet et al. (2010), persons diagnosed with FAD have a higher incidence of psychotic symptoms, such as hallucinations and delusions, in comparison to those diagnosed with SAD.

The similar pathological phenotypes of FAD and SAD can be diagnosed through clinical assessment and cognitive evaluation. The deposition of Amyloid- β (A β) and hyperphosphorylated tau protein can be screened using biomarker detection, as shown in Figure 1. The NFTs and senile plaques resulting from the action of these two proteins are often examined through imaging techniques such as structural magnetic resonance imaging (MRI) or positron emission tomography (PET).

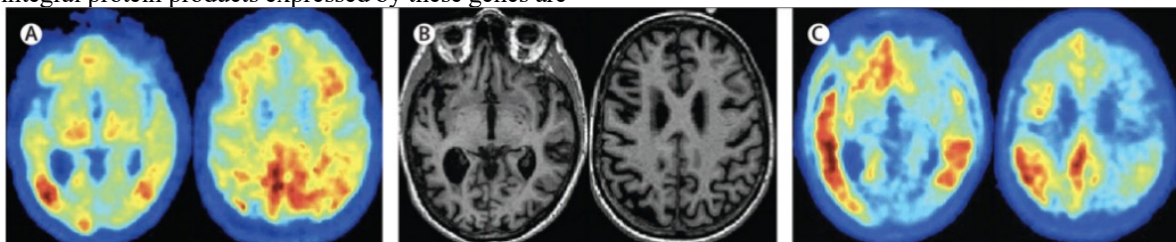


Figure 1 Imaging Features of an Alzheimer's Patient [12] (A) Amyloid Pittsburgh compound B-PET scan displaying predominant amyloid deposition in the posterior cingulate region. (B) T1-weighted MRI images exhibiting generalized cortical atrophy from left to right. (C) Tau-PET image employing an AV1451 tracer, revealing left-sided inferotemporal lobe, parietal, and mild posterior cingulate deposition of tau.

Nevertheless, there are variations in the initiation, advancement, and intensity of symptoms between FAD and SAD. According to Schon and Area-Gomez [16], FAD tends to manifest at an earlier age, often before individuals reach 65 years old, while SAD commonly emerges later in life. According to Sweet et al. (2010), persons with FAD often have a faster development of symptoms compared to those with SAD [15]. This accelerated deterioration in cognitive function is seen in FAD cases. Moreover, it has been shown that FAD has a more pronounced phenotype, characterized by more severe cognitive impairment and a higher incidence of psychotic symptoms [15].

2.3. Pathological Changes

The pathological characteristics of both SAD and FAD are closely associated with the deposition of A β and hyperphosphorylated tau protein, leading to the formation of neurofibrillary tangles (NFTs). These abnormal aggregates contribute to the formation of senile plaques and neurofibrillary tangles in the brain, which are among the typical pathological features of AD [17].

Additionally, a research by Ochalek et al. utilized induced pluripotent stem cells (iPSCs) derived from patients with Familial Alzheimer's Disease (FAD) and Sporadic Alzheimer's Disease (SAD) to investigate the pathological mechanisms of these forms of AD. They found no significant differences in the hyperphosphorylation of tau protein between FAD and SAD iPSC-derived neurons [18]. In terms of animal models [11], the 3xTg-AD transgenic mouse model is commonly employed for AD research and represents a model for FAD. This model harbors mutations in PSEN1, APP, and tau genes. (Similarities and differences exist

between this transgenic model and the non-transgenic AD mouse model known as ICV-STZ mice.) A comparison between these two models revealed similarities in cognitive impairment and maze learning deficits [9]. Xiaozhen Li conducted an observation of modifications in white matter (WM) that are linked to changes in CSF fluid, which aligns with prior findings in sporadic AD [17].

The clinical course of FAD may differ from Late-Onset SAD, as some studies suggest that symptoms progress more rapidly, leading to shorter survival times [19]. Variations may exist in the distribution and composition of A β species between Sporadic AD and Familial AD. A research conducted by Dinkel et al. revealed that there was no substantial disparity in the overall β -amyloid protein pattern between sporadic Alzheimer's disease and familial Alzheimer's disease, the load of specific β -amyloid peptides differed. Within the frontal cortex, compared to Familial AD, sporadic AD exhibited increased deposition of β -amyloid 1-38 and 1-43, while the load of β -amyloid 1-42 decreased [20]. Table 1 shows the comparison of Familial AD and Sporadic AD. Shinohara et al. made an additional observation in the context of SAD, namely that there was a disproportionate accumulation of β -amyloid-b42 in cortical areas compared to FAD. This accumulation was shown to be strongly associated with the typical regional distribution of PSD 95 [21].

In the realm of animal models, Chen et al. compared mice models of FAD with models of general AD in order to discern differences in potential mechanisms and neuropathological features. They indeed noted disparities in these aspects [11]. In a study conducted by Ochalek et al., iPSCs obtained from individuals suffering with FAD and SAD were employed to investigate the pathological mechanisms of these AD forms. They did observe differences in the secretion levels of A β 1-40 [18].

Table 1. Comparing Familial AD and Sporadic AD

	Familial AD	Sporadic AD
Related Genes	PSEN1, PSEN2, APP	APOE ϵ 4, CLU, SORL1, ABCA7, TREM2
Gene Function	Crucially contribute to brain amyloid-beta plaque formation	Participate in numerous processes related to A β metabolism
Primary Causes	Mutations in crucial genes	Intricate interaction among genetic, environmental, and metabolic elements.
Percentage Share	Less than 1-5%	Over 95%
Clinical Characteristics	Usually before the age of 65 Accelerate, resulting in reduced survival times. Higher incidence of psychotic symptoms	Typically observed in elderly age. A progressive decline in cognitive functioning, including memory impairment, and a reduction in the ability to perform everyday activities
Pathological Changes	SAD and FAD share pathogenic features, including A β deposition and hyperphosphorylated tau protein production, resulting in neurofibrillary tangles (NFTs). Sporadic AD showed higher deposition of β -amyloid 1-38 and 1-43 in the frontal cortex compared to familial AD, although β -amyloid 1-42 burden reduced.	

3. Discussion

Throughout the studies, the probability of developing Alzheimer's disease in older adults with family aggregation is much higher than in sporadic cases, indicating that family history is a strong contributor to the development of AD. The main, but not the only, genetic trigger for familial

AD is mutations in the progerin gene. The APOE has a significant effect on sporadic AD, mainly due to the polymorphism and heterogeneity of the gene, with three alleles present at the same locus. The three alleles have different effects on the incidence of sporadic AD, with the first one being a risk element for SAD, and the last two genes being able to reduce the incidence of sporadic AD. The first gene is one of the dangers of sporadic AD, while the next two genes reduce the incidence of sporadic AD.

Preventive measures: (1) Prenatal screening. Since FAD is inherited in an autosomal dominant manner, prenatal screening for Down's syndrome can effectively avoid the risk of future morbidity. (2) Community-based prevention. Build a perfect urban and rural public health system, establish professional elderly care organizations and provide professional service training, and strengthen the development of community services. We should popularize the knowledge of Alzheimer's disease through lectures and other forms, so as to strengthen the elderly's knowledge of their own physical condition. (3) Drug prevention. At present, statins are mainly used in the process of drug prevention to reduce the incidence of AD in the elderly by affecting the lipo vacuolar microregion and brain-derived neurotrophic factor. (4) Nutrient intake. After experimental analysis, it is found that the pathogenesis of AD is related to mitochondrial genes, and the damage of RNA in mitochondria will make the mitochondria lack of antioxidant ability, so we can improve the antioxidant ability of the human body through the intake of nutrients from the outside world, such as taking vitamin E, carotene, vitamin C, and aromatic amines. Tocopherol, also known as vitamin E, is a lipophilic antioxidant. By taking vitamin E, the human body can protect the lipid structure of the human body, such as cell membranes, so as to realize the inhibition of oxidative stress. Vitamin C can play the same role as vitamin E in a hydrophilic environment; meanwhile, carotenoids have a strong antioxidant effect, and they can inhibit the oxidative stress and inflammatory damage of the brain. The retinal desmoplakic pigment is established by carotene, which can improve the visual acuity of human body, enhance the precise vision, make the human brain receive more external information, and reduce the cognitive load of the human brain. Nutrients such as vitamin C and vitamin E should be supplemented to enhance the metabolism activity of free radicals, improve the biochemical repair ability of cells, reduce the damage of the oxidative enzymes of gene mutation to the human brain, and lower the prevalence and onset of AD to reduce the risk of AD.

4. Conclusion

The literature review offers a comprehensive examination of the genetic pathways, clinical characteristics, and pathological alterations associated with familial AD and sporadic AD.

Familial AD is linked to genetic abnormalities in certain genes, including APP, PSEN1, and PSEN2. These mutations lead to the synthesis of atypical protein variants that participate in the formation and buildup of amyloid-beta. In contrast, it should be noted that SAD mostly manifests as an irregular occurrence of the ailment. This sporadic form of the illness is linked to genetic predispositions, including the APOE ϵ 4 allele, as well as mutations in genes such as CLU, SORL1, and TREM2. These genetic variables have been shown to be connected to modifications in the metabolism and elimination of A β .

Both FAD and SAD are characterised by cognitive decline, including memory loss and difficulty in everyday activities. Nevertheless, FAD has a tendency towards an

earlier start, a more accelerated course, and a higher degree of symptom severity when compared to SAD. Psychotic symptoms, such as hallucinations and delusions, have a higher prevalence in individuals diagnosed with FAD. On the other hand, sporadic Alzheimer's disease (SAD) is distinguished by a delayed initiation and a more progressive deterioration in cognitive functioning.

Both familial AD and sporadic AD are distinguished by the presence of amyloid-beta (A β) plaques in the brain. Nevertheless, FAD has a more robust correlation with A β plaques, while SAD encompasses other pathological alterations including neurofibrillary tangles and neuronal depletion.

To date, the genetic factors described cannot comprehensively elucidate the pathological physiology of AD. In fact, the heterogeneity in clinical diagnosis of AD, as unveiled through neuropathology, neuroimaging, clinical assessments, and biomarkers, cannot be solely attributed to separate investigations of Familial AD and Sporadic AD.

Acquiring a comprehensive comprehension of the parallels and distinctions between these two variants of AD would enhance the precision and individualization of strategies used in the early detection and management of AD. Future research should persist in exploring the molecular mechanisms underpinning FAD and SAD, thereby fostering effective interventions and management strategies for AD.

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