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Clinical phenotypes in autossomal dominant Alzheimer`s disease

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Resumo

Introdução

A Doença de Alzheimer (AD) é a principal doença neurodegenerativa do sistema nervoso central causadora de demência, cuja etiologia é multifatorial, englobando fatores ambientais e genéticos. Diversos processos celulares e metabólicos (incluindo deposição amilóide, hiperfosforilação *tau* e ativação da micróglia) levam à morte neuronal e diminuição do fluxo sinático.

A AD divide-se na forma esporádica (sAD) e familiar (fAD), sendo a primeira a mais prevalente (99% dos casos de AD) e fAD correspondendo a 1% dos casos de AD.

Objetivos

Realizar uma revisão acerca da relação entre as diferentes mutações genéticas conhecidas e fenótipos clínicos da fAD, tendo em conta a idade de início da doença, morbimortalidade, prognóstico e variantes clínicas em cada uma das mutações genéticas supramencionadas. Pretende-se ainda rever os processos fisiopatológicos associados aos genes mutados associados à fAD.

Metodologia

A presente revisão pretende resumir as diferenças entre os genótipos e fenótipos relacionados na doença de Alzheimer's familiar autossómica dominante (ADfAD). Deste modo, para a realização desta tarefa foi realizada uma pesquisa bibliográfica na base de dados Pubmed, selecionando artigos publicados nos últimos 20 anos, em inglês, ao pesquisar por termos MeSh (Medicals Subject Headings) relacionados com ADfAD, as suas mutações, fisiopatologia e sintomas clínicos.

Resultados

A doença de Alzheimer familiar é uma forma rara de AD, que tem manifestações clínicas, para além da perda progressiva da memória. A maioria dos casos de AD apresentam-se tipicamente com défice amnésico progressivo, com início acima dos 65 anos (AD de inicio tardio), correspondendo na sua larga maioria às formas esporádicas de AD. Por oposição, a fAD está associada a um conjunto de manifestações cognitivas mais heterogéneas, geralmente tem uma idade de início mais precoce e um curso da doença mais agressivo. Existem 3 genes descobertos até à data cujas mutações estão relacionadas com o metabolismo de β-amilóide, e, consequentemente na fisiopatologia da fAD: presenilina-1 (PSEN-1), presenilina-2 (PSEN-2) e proteína precursora da amilóide (APP).

A fAD difere da sAD, quanto à progressão fisiopatológica, atingimento topográfico do córtex cerebral e, consequentemente, apresenta um amplo espectro de manifestações clínicas. Entre os 3

diferentes genótipos da fAD, PSEN-1 é o mais comum e existem algumas diferenças fenotípicas entre os mesmos, como por exemplo, a PSEN-2 apresentar uma idade de início mais tardio.

Conclusões

Até à data, a fisiopatologia da AD permanece pouco clara, explorar a base genética e patológica da fAD pode iluminar aspectos do mecanismo da doença subjacente e provavelmente servirá de ajuda à compreensão e tratamento da AD no futuro.

Palavras-chave: Doença de Alzheimer autossómica dominante; Doença de Alzheimer de início precoce; PSEN1; PSEN2; APP.

Abstract

Background

Alzheimer´s disease (AD) is the main neurodegenerative disorder of the central nervous system that cause dementia, whose etiology is multifatorial, encompassing environmental and genetic factors. Several cellular and metabolic processes lead to neuronal death and synaptic flow decrease. Neuropathological studies showed amyloid deposits, neuritic plaques and neurofibrillary tangles at the microscopic level and, macroscopically, cerebral tissue atrophy.

AD is divided into sporadic Alzheimer's Disease (sAD) and familial Alzheimer's Disease (fAD), the first being the most prevalent (99% of AD cases) and fAD corresponding to less than 1% of AD total cases.

Objectives

To carry out a review of the relationship between the different known genetic mutations and clinical phenotypes of fAD, taking to account the age of onset of the disease, morbidity and mortality, prognosis and clinical variants in each of the aforementioned genetic mutations. Additionally, to review pathophysiological processes associated to the disease associated mutated genes.

Methods

The present review will summarize the differences between the 3 genotypes and the resulting phenotypes in autossomal dominant familial Alzheimer's Disease (ADfAD). Therefore, in order to carry out this task a bibliographic research was made using Pubmed's database, selecting articles published in the last 20 years, in English, searching for MeSh (Medicals Subjects Headings) terms related with ADfAD, the mutations involved in the pathophisiology and the clinical symptoms.

Results

Familial Alzheimer's disease is a rare form of AD with clinical phenotypes beyond progressive memory impairment. The majority of AD cases has a clinical presentation limited to progressive amnesic dementia, classically aged> 65 years old, corresponding to late onset Alzheimer's disease (LOAD), almost entirely embracing cases of sAD. Contrary, fAD is associated with a wider range of clinical manifestations, often begins on earlier ages at onset (AAO) and na agressive course compared to the sporadic form. There are 3 genes discovered to date whose mutations influence the β-amyloid metabolism, being responsible for the etiology of fAD: presenilin-1 (PSEN-1), presenilin-2 (PSEN-2) and amyloid precursor protein (APP).

The fAD differs from the sporadic counterpart regarding physiopathological progression and preferential topographical of brain involvement, consequently, having a wider range of clinical manifestations. Among the 3 different genotypes of fAD, PSEN-1 is the most common and there are some phenotypic differences between them, for example, PSEN-2 has a later age of onset.

Conclusions

To date, the pathophysiology of AD remains unclear, exploring the genetic and pathological basis of fAD can illuminate aspects of the underlying disease mechanism, and is likely to inform our understanding and treatment of AD in the future.

Keywords:autossomal dominant Alzheimer's disease; early-onset Alzheimer's disease; PSEN1; PSEN2; APP

Abreviations list

AchI – Acetylcholinesterase inhibitors

AAO – age at onset

Aβ – β-amyloid

ABCA1 – ATP-binding cassette transporter 1

ABCA7 – ATP-binding cassette transporter 7

AD – Alzheimer's disease

ADEOFAD – Autossomal dominant early-onset familial Alzheimer's disease

ADfAD – Autossomal dominant familial Alzheimer's disease

APP – amyloid precursor protein

BIN1 – Bridging Integrator 1

BPSD – Behavioral and psychiatric symptoms of dementia

CAA – cerebral amyloid angiopathy

CNS – Central Nervous System

EOAD – Early-onset Alzheimer's disease

F-FDG-PET – Fluorodesoxiglicose Pet scan

fAD – Familial Alzheimer's disease

LOAD – Late-onset Alzheimer´s disease

PIB PET – Pittsburg compound B PET scan

PCR – Polymerase Chain Reaction

PSEN1 – Presenilin 1

PSEN2 – Presenilin 2

sAD – Sporadic Alzheimer's disease

TREM2 – triggering receptor expressed on myeloid cells 2

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Table List

Background

Alzheimer's disease, the commonest cause of dementia, is a progressive neurodegenerative disease recognised by the World Health Organisation as a global public health priority, with huge implications for individuals and society. As the population across the globe ages, the incidence and prevalence of age-related diseases is rising[1], such as dementia, defined as an acquired progressive cognitive impairment sufficient to impact on activities of daily living, resulting as a syndrome including memory and intelectual loss, behavioral modifications and incapacity to conclude complex tasks[2]. Despite large gains in the understanding of AD pathogenesis there are no disease-modifying treatments, only symptomatic ones.

AD is divided into sporadic Alzheimer's Disease (sAD) and familial Alzheimer's Disease (fAD), the first being the most prevalent (99% of AD cases) and fAD corresponding to <1% of AD total cases.

Similar to sAD, there is no disease-modifying treatments for familial Alzheimer's Disease. Anti-AD pharmacoterapies (AchI i.e. donepezil, galantamine, rivastigmine, memantine) provide modest but meaningful benefits by delaying disability and reducing clinical progression[3]. Similar to sAD, some fAD cases have insidious onset of episodic memory symptoms but it often differs clinically due to its distinctive features, namely early age at onset (AAO), often in between 35-55 years old, faster development of the disease and more agressive course with increased morbidity and mortality[4]. Therefore, a multidisciplinary approach and simptomatic targeted treatment should be implemented.

Regarding genetics, and in opposition to sAD that has no evidence to show an increased risk for the offspring to develop the disease, fAD is commonly transmited to the offspring (with 50% chance) because the mutations in the genes responsibles for fAD are transmitted in an autossomic dominant way. It also differs from the first in genotypes, in pathophysiological progression, cerebral cortex topography and, consequently, clinical characteristics, demonstrating a wider spectrum of manifestations. There are three genes discovered to date whose mutations are involved in the pathophysiology of fAD: presenilin-1 (PSEN-1); presenilin-2 (PSEN-2) and amyloid precursor protein (APP)[5]. All these mutations are related with β-amyloid metabolism. The amyloid cascade is the most accepted theory in the scientific community at the origin of the pathophysiology of AD, resulting from the imbalance in the production and clearence of β-amyloid[6].

The present review will summarize the differences between the 3 genotypes and the resulting phenotypes in autossomal dominant familial Alzheimer's Disease (ADfAD). Therefore, in order to carry out this task we selected experimental and review studies from Pubmed database, searching for MeSh

(Medicals Subjects Headings) terms related with ADfAD, the mutations involved in the pathophisiology and the clinical symptoms.

Familial Alzheimer's Disease

AD is divided into sporadic Alzheimer's Disease (sAD) and familial Alzheimer's Disease, the first being the most prevalent (99% of AD cases) and fAD corresponding to <1% of AD total cases[1]. The majority of AD cases has a clinical presentation limited to progressive amnesic dementia, classically aged> 65 years old, corresponding to late onset Alzheimer's disease (LOAD), almost entirely embracing cases of sAD. In rarer situations, the disease can manifest at earlier onset ages (<65 years), corresponding to early onset Alzheimer's disease (EOAD), which comprises about 5% to 6% of cases of AD, where about 20% of cases correspond to familial Alzheimer's disease (fAD), representing a much higher genetic predisposition then LOAD[7].

FAD is transmitted to the offspring in an autossomal dominant way[8], resulting from pathogenic mutations in one of the three identified genes responsible for the disease: PSEN-1; PSEN-2 and APP. The APOε4 allele is related with the sporadic form of AD, but not causative[9]. Currently it is believed that APOε4 is a risk factor for both sAD and late-onset fAD[10]. In both sporadic and familial AD, the possession of APOε4 allele is associated with decreased AAO.[11] Many other molecular factors (i. e. immunological cause (TREM2) with lipid disorder (ABCA1, ABCA7), metabolites transport (BIN1)) can be related to the pathophisiology of AD, including β-amyloid depposition, *tau* hyperphosphorylation, microglia activation and neuroinflammation[12], being the amyloid cascate theory the most accepted in the scientific community to explain the pathophisiology of AD[13]. Still, it remains uncertain if the neuropathology and molecular processes are the same for sAD and fAD cases. It is also believed that epigenetic has a role in fAD because the heterogeneity of clinical manifestations. Despite the neurodegenerative processes of both forms of AD appears to be similar, it is thought that the physiopathology of fAD differs form sAD by the excess production of β-amyloid (Aβ42, Aβ40), whereas in sAD it is thought to be related to the lack of β-amyloid clearence. Aβ42/Aβ40 ratio may also varie amongst these different fAD gene mutations with different clinical repercutions[5], but, overall, it is commonly increased. Pathological studies have demonstrated that the proportion of brain tissue occupied by Aβ42-containing plaques is significantly higher in fAD than sAD.

Macroscopically, in both forms, cerebral atrophy is observed, with neuronal loss and diminished synaptic flow. Similarly, studies have shown extracellular β-amyloid depposition in the brain parenchyma, neurofibrillary tangles and neuritic plaques in both AD forms. It is believed that β-amyloid deposition starts around 20-25 years before onset of symptoms in cases of fAD[1]. In sAD the time between β-amyloid accumulation and clinical symptoms remains to be quantified, but current theories suggest that this time may be for more than a decade[14]Primitive β-amyloid deposits were

more frequently distributed in regular clusters and less frequently distributed in large clusters in fAD compared with sAD.[15]

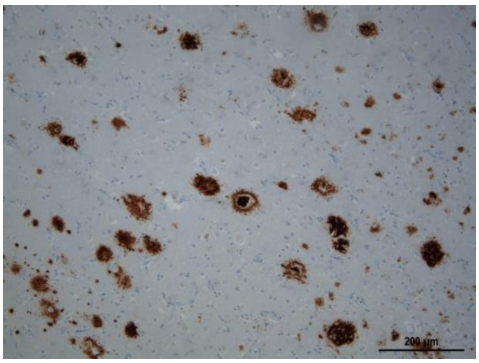

Figure 1 – Parenchymal beta-amyloid deposits (globose diffuse and mature plaques) in neocortex (Portuguese Brain Bank archive). Scale bar: 200µm

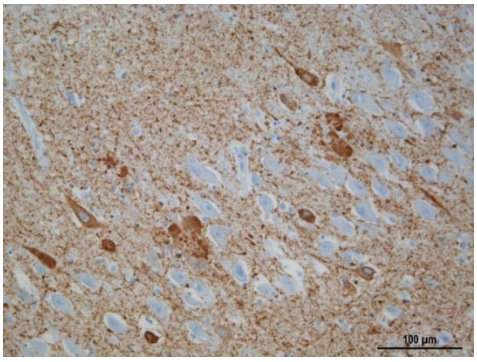

Figure 2 – Tau pathology (neurofibrillary tangles, neuritic plaques and dystrophic neurites) in the hippocampus (Portuguese Brain Bank archive). Scale bar: 200µm

Classically, in sAD patients the medial temporal lobe structures are most affected, with progressive memory loss as main clinical manifestation. In fAD cases many clinical manifestations, called variants (behavioral EOAD, disexecutive EOAD, aphasic variant, posterior cortical atrophy) occur according to the cerebral topography preferential involvement of the pathology. The hippocampus may be spared in an early stage of some of these variants[5].

Compared to sAD the course of fAD variants seems to be more agressive, and presents an age at onset (AAO) aproximately 20 years earlier (AAO=35-55years). The commonest variants of fAD in descending order are logopenic variant primary progressive aphasia, posterior cortical atrophy, behavioral/disexecutive variant and the acalculic variant[6]. Most of fAD cases result from PSEN1 mutations (>75%), APP mutations are responsible for nearly 15-20% of autossomal dominant early

onset familial Alzheimer's disease (ADEOFAD) and the rarest PSEN2 mutations related correspond to <5%.[16]

The management should be multidisciplinary and directed to the symptoms accordingly to each variant and genetics testing and counseling should be done in all fAD cases[4]. Recently, for diagnosis of fAD, a genetic testing has been advocate in the presence of an EOAD patient with family history of one relative with early onset dementia[17].

Presenilin-1

PSEN1 gene is located in chromossome 14q24.3[18], and it is a vital component of the γ-secretase complex, which cleaves APP into Aβ fragments.[19] Mutations in PSEN1 account for up to 75% of fAD, with complete penetrance and early age of onset.[20] Mutant γ-secretase increases Aβ42 level while it decreases Aβ40 level, leading to an increased Aβ42/Aβ40 ratio. Morphologic variants in Aβ plaques due to PSEN1 mutations may result in cotton wool plaques[19]. Cotton wool plaque is formed by large rounded Aβ deposits, and it tends to be immune-positive for Aβ42, rather than for Aβ40[21]. PSEN1 mutations are often missense mutations, but deletions and insertions have also been detected. To date, around 300 pathogenic mutations have been identified in PSEN1, of which 70% mutations occur in exons 5, 6, 7 and 8[5]. The mutations are present in gnomAD database (https://gnomad.broadinstitute.org) or jMorp (https://jmorp.megabank.tohoku.ac.jp).

Regarding the cerebral topography, EOFAD with PSEN1 mutations involve multiple regions, mainly the neocortex, beyond the hippocampus and with subcortical affection, marked depigmentation of the substancia nigra and locus coeruleus[22]. Atrophy of the pyramidal tract portion at medula oblongata and Aβ deposits in the cerebellum have also been identified[19]. Cerebral amyloid angiopathy was also noted in some cases. The cognitive profile has so far predominantly shown amnestic and cognitive symptoms typical of dementia, but may present with some unusual clinical features, in particular spastic paraparesis[23] and epileptic seizures[5]. EOAD with PSEN1 mutations can present extrapyramidal signs, behavioral features suggestive of frontotemporal dementia[24], language impairment and cerebellar ataxia, but also behavioral and psychiatric symptoms of dementia (BPSD) like anxiety, hallucinations and delusions[25]. However, almost all these symptoms having been also reported in sAD cases.

EOFAD with PSEN1 mutations typically have an AAO in the early 40s, ranging from 35 to 65 years. The course of the disease and the clinical manifestations may change accordingly to specific PSEN1 mutations (see table 1), but there is no evidence to support a specific mutation-related phenotype. The disease duration varies from 5 to 15 years[5].

Mutation	Age at onset	Age at death	Disease duration	Symptoms
Val97Leu	36.5	52.4	15.9	Memory disturbance, dyscalculia, apathy and personality changes
Ile167del	38	55	15.5	Memory decline, disorientation, spastic paraparesis and behavior variants
Leu226Arg	60	-	-	Language disability, memory decline and personality change, irritability
Met233Leu	40.6	44.8	4.2	Progressive memory decline, seizures and paralysis
Phe388Leu	43	44.4	1.41	Progressive memory decline, psychosis and paranoid delusions
Ala434Thr	35	55	8	Progressive memory decline, hallucinations and delusions

Table 1 – Examples of PSEN1 mutations and its clinic variants. Adapted from Quin *et al*[5].

Presenilin-2

PSEN2 gene is located on chromossome 1q31-q42[26], and its mutations are very rare, to date 33 pathogenic PSEN2 mutations have been detected worlwide[5]. PSEN2 is a main component of the γ-secretase complex along with PSEN1, nicastrin, Aph-1, and PEN-2[27]. Pathophisiologically, PSEN2 mutations change the γ-secretase activity and leads to elevation of Aβ42/Aβ40 ratio, similarly to the PSEN1 mutation. Although, in PSEN2 mutations less amyloid peptide is produced then in PSEN1 mutations, besides the close homology. Neuritic plaque formation and neurofibrillary tangle accumulation may be seen as neuropathological changes in some people with PSEN2 mutations[17].

Regarding EOFAD with PSEN2 mutations cerebral topography of involvement, imaging studies in these patients using PIB PET and F-FDG-PET showed amyloid deposits and hypometabolism[28], respectively, in frontal, temporal, parietal and insular lobes, cingulate cortex, precuneus, caudate nucleus, striatum and thalamus, alongside with general cortical atrophy (hippocampus included).

PSEN2 mutations are the least common of the three genes known to cause fAD, and therefore literature is relatively scant. The proeminent symptoms of these patients is memory impairment, commonly associated with language impairment, depression, personality changes, parkinsonism and myoclonus, paranoia, visual hallucinations and agitation[29] (see table 2).

Compared to PSEN1 mutation carriers, PSEN2 mutation carriers have a later AAO, commonly in the early 50s, ranging from 35 to 65 years and the course of the disease seems to be more indolent[30], the duration of the disease appears to range from 10 to 20 years.

Mutation	Age at onset	Disease duration	Symptoms
Lys82Arg	50	-	Speech difficulties and depressions
Prol123Leu	57	-	Parkinsonism, myoclonus and personality changes
ASN141tYR	46	16	Speech dificulties, paranoia, visual hallucinations and agitation

Table 2 – Example of PSEN2 mutations and its clinic variants. Adapted from Quin *et al*.[5]

Amyloid precursor protein

The gene encoding APP is located on chromossome 21q21.3[23]. It is the second most common mutation of the three, and to the date 63 pathogenic mutations in APP gene were detected worlwide. APP is a transmembrane protein, which plays a role in synaptic plasticity[31]. Three enzimes have cleavage sites in APP: α-, β- and γ-secretases. Proteolysis of APP by α- and γ-secretases results in nonpathogenic fragments (sAPPα and α-C-terminal fragment) in nonamyloidogenic pathway. In amyloidogenic pathway, abnormal cleavage of APP by β- and γ-secretases could result in two major Aβ precursors that include sAPPβ and β-CTF. The action of γ-secretases on β-CTF generates Aβ extracellularly that deposits in the neuron in AD patients. Physiopatologically, different mecanisms occur from mutation to mutation, since the destruction of Aβ40 cleavage site to increased γ-secretase action in Aβ42 location, all leading to an increased Aβ42/Aβ40 ratio. Aβ42, Aβ40 and Aβ42/Aβ40 ratio have been established as the most important biomarkers for AD[5].

In terms of cortical topography of hypometabolism and cerebral atrophy, APP-related fAD does not differ much form the others fAD mutations.[32] Hippocampal sparing and greater posterior neocortical involvement is reported. Involvement of white matter tracts in posterior association areas and frontoparietal networks are characteristics that differ mainly from sAD areas (mainly neocortex).[33] Cerebral amyloid angiopathy (CAA) with microhemorrhages is reported often in studies with APP-related fAD brains, consequently present focal neurological signs, such as aphasia.[34]

The commonest clinical manifestation is progressive memory impairment, followed by rapid progression to severe dementia within 5-10 years. The AAO is around 46-55 years and it varies according to specific mutations (see table 3).[35]

Mutation	Age at onset	Age at death	Diese duration	Symptoms
Asp678His	50.6	58.5	7.9	Progressive memory decline, restlessness, persecutory delusions, self-talking and slurred speech
Val715Met	45	48	3	Memory decline, bradykinesia and irritability
Ile716Thr	35-40	-	-	Progressive memory decline, aphasia and increased muscular tension
Val717Ile	54.7	67.1	11.7	Executive dysfunction, disorientation, spastic paraparesis and cerebellar ataxia
Met722Lys	42.8	58.9	16.1	Memory decline, executive dysfunction, disorientation, aphasia and depression
Lys724Met	46.6	53.4	6.8	Verbalization, executive dysfunction, sluggishness and apathy

Table 3 – Examples of APP mutations and its clinic variants. Adapted from Quin *et al*.[5]

Early-Onset Alzheimer's Disease

Early Onset Alzheimer's Disease (EOAD) is defined as having an AAO younger than 65 years. The overall clinical profile of EOAD differs from that of LOAD. A higher proportion of patients with EOAD present symptoms such as language, visuospatial or dysexecutive phenotypes rather than the usual amnestic disorder seen in LOAD and have a genetic predisposition, being 20% of EOAD diagnosed with fAD. In amnestic EOAD a higher frequency of APOε4 allele was verified, while the APOε4 allele frequency in variants is less observed[6].

There is no scientific evidence showing an increased probability of the offspring get the disease in sAD cases, contrarily to fAD. The risk is higher in both forms when in the presence of APOε2, APOε3 or APOε4 gene mutation.

Patients with AAO earlier than 35 are classified as very early-onset Alzheimer's Disease (VEOAD), which are associated with more agressive course of the disease and increased mortality, being the majority of cases, fAD cases[36].

Conclusions

AD is the commonest cause of dementia worldwide and it is divided in two forms, sporadic (sAD) and familial (fAD). Although fAD represents a much lesser number of cases (aproximately 1%), severe features like earlier AAO, more agressive course of the disease and ealier age of death shows the importance of correct management and treatment. To do so, a better understanding of the pathophisiology with more studies to characterize the variant phenotypes and correlate genotypes, are needed. The comparison between the two AD forms is relevant, in order to recognize similarities and differences between both forms and gain insights into the cascade of pathological events and how they relate to clinical manifestations. To the date studies have shown main differences in pathophisiology such as higher ratio Aβ42/Aβ40 in fAD, different mechanisms in the amyloidogenic pathway that leads to an increased production of Aβ42 in fAD and a decreased clearance of Aβ40 in sAD. Additionally, fAD show more commonly hippocampal sparing and less mesial temporal lobe disease, and a greater posterior neocortical atrophy (parietal and temporoparietal junction) and hypometabolism. Consequently, fAD has an overall less semantic memory impairment and greater attention, executive, praxis, visuospatial and psychosocial difficulties (more associated with depression and anxiety) compared to sAD.

The main similarities reported to date clinically and pathophysiologically are, respectivelly, progressive memory and cognitive impairment, and amyloid deposition, *tau* hyperphosphorilation, neurofibrillary tangles, a common amyloidogenic pathway, same relationship between Aβ deposition and APOε genotype (APOε4 allele possession is associated with decreased age at onset in both sporadic and familial AD), decreased synaptic flow, neuronal hypometabolism and cortical atrophy.

To date, the pathophysiology of AD remains unclear, exploring the genetic and pathological basis of this phenotypic heterogeneity can illuminate aspects of the underlying disease mechanism, and is likely to inform our understanding and treatment of AD in the future.

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