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Alzheimer Disease Genetic Heterogeneity: Its Importance in Every Aspect of the Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease and it still incurable [1]. Late-onset Alzheimer disease (AD) is the most frequent form of dementia. The genetic findings of early onset AD are different from the late onset disease. Although cases of familial AD (early onset) present a small prevalence, they can help to identify genetic patterns of the disease, those cases have been associated with autosomal dominant mutations in the genes *PSEN1*, *PSEN2*, and *APP*. The ε4 allele of the apolipoprotein E (*ApoE*) gene is the most known gene linked to late-onset AD. The mutations of *APP*, *PSEN1*, and *PSEN2* account for 5 to 10% of early-onset AD, while the *ApoE* ε4 allele increases the risk of early and late-onset AD. However, this mutation is not sufficient for the AD onset. There are many genes being traced, once they present functional similarities compared to those already known. Most of these genes are related to three pathways: inflammation and immune response, lipid metabolism and intracellular trafficking. Those genes are discussed in this article and are also related with specific image exams findings, cerebrospinal fluid alterations and with the disease clinical manifestations evolution. In sum the genetic it's probably the most important field to understand the AD development, so studying the genes related to this disease is extremely important to understand the physiopathology involved with the disease.

Keywords: *Alzheimer; Disease; Genetic and Mutation*

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease and it still incurable [1]. Late-onset Alzheimer disease (AD) is the most frequent form of dementia. Late-onset AD is characterized by symptoms starting after 60 years old and is marked by a slow evolution, from mildly impaired memory function to severe cognitive loss, evolving to a complete incapacity and death [2]. Its physiopathology is under discussion, but the deposition of toxic proteins complexes is thought to be the origin of the progressive central nervous system (CNS) damage. AD is more recurrent within families when compared to patients without background. Therefore, the genetic is showing to be a crucial aspect for the disease [3]. There is some progress in identifying genes associated with the AD. AD is marked by the deposition of amyloid plaques and neurofibrillary tangles, which are responsible for the impairment of neuronal function and can lead to neuronal death [1,16]. Intracellular changes are an important part of the disease, once they are more specific than the deposition of amyloid plaques. Those changes include abnormal hyperphosphorylated tau protein deposits (a protein constituent of microtubules). The activation of microglia and neurons/synapses loss is widespread [2].

Methods

We performed a literature review using PUBMED. We used Alzheimer, Disease, Genetic and Mutation as our key words. The search was limited to the studies published in English, from 2010 to 2018. We raised a total of 68 articles, but only 20 had the data that interested us.

We observed the genetic factors that were related with AD development. Due to retrospective design of this literature review, we did not apply for ethics committee approval.

Early onset AD genetic findings

The genetic findings of early onset AD are different from the late onset disease. Although cases of familial AD (early onset) present a small prevalence, they can help to identify genetic patterns of the disease, those cases have been associated with autosomal dominant mutations in the genes presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and the amyloid precursor protein gene (*APP*). These mutations have been related to the accumulation of toxic amyloid β protein (Aβ) ($A\beta_{1-42}$), what would lead to the aggregation and accumulation of the amyloid plaques, which has been considered the cause of AD. The $A\beta_{1-42}$ peptide is originated after the cleavage of *APP* by proteolytics enzymes, such as α, β, and γ-secretases. The *PSEN1* and *PSEN2* mutations have been showing to impair the pathway of γ-secretase, what leads to an increased production of $A\beta_{1-42}$ [1-3,6-11,13,18].

APP is located at chromosome 21q21 and is responsible for encoding a transmembrane protein. Most of *APP* are cleaved by α- and γ-secretases, within the Aβ domain, leading to non-toxic substrates, such as *sAPPα* and a C-terminal fragment (CTF). However, after this cleavage *APP* may undergo a consecutive proteolytic cleavage by β- and γ-secretases, this process leads to the production of amyloidogenic substrates, such as Aβ40 and 42 peptides, *sAPPβ* and β-CTF. Dominant mutations in *APP* represents approximately 14% of early-onset AD cases. The duplication of *APP* leads to a classic AD with cerebral amyloid angiopathy. Individuals presenting Down Syndrome (trisomy 21) develop AD neuropathology. However, individuals presenting partial trisomy of chromosome 21, not including the *APP* gene doesn't develop clinical or neuropathological AD [1-3,6-12,18]. Therefore, these evidences shows the importance of *APP* gene for the early-onset AD.

PSEN1 and *PSEN2* are located at the endoplasmic reticulum and Golgi apparatus and are part of the γ-secretase complex. Mutations in *PSEN1* and *PSEN2* can exert their effects by affecting γ-secretase function, once they inhibit the initial endoproteolytic cleavage, what leads to the release of *APP's* intracellular domain. They can also cause an early release of intermediary products of *APP* during γ-secretase processing, what generates longer Aβ peptides; they can lead to a preferential cleavage of *APP* at position 49-50 or 51-50. *PSEN1* is located at 14q24.3. Its dominant mutations are responsible for approximately 80% of early-onset AD cases. *PSEN2* is located at 1q31-q42. Its dominant pathogenic mutations are responsible for 5% of early-onset AD cases. Late-onset AD cases are also related with dominantly inherited mutations in *PSEN1* and *APP*. These families probably carry additional genetic mutations that are responsible for the delay age at onset of the clinical manifestations [2,3,6-9,12,13,18]. However those genes are also important to the construction of a genetic profile for the AD patients.

Late onset AD genetic findings

The ε4 allele of the apolipoprotein E (*ApoE*) gene is the most known gene linked to late-onset AD [1,6-12]. *ApoE ε*4 allele is located on chromosome 19q13. *ApoE* encodes a glycoprotein synthesized in the liver (most of it), brain and also by other cells, like macrophages and monocytes. *ApoE* participates of cholesterol mobilization and redistribution during neuronal growth and repair. It also contributes for the nerve regeneration, immunoregulation and activation of several lipolytic enzymes [2,3,7,9,14]. According to Basavaraju., *et al.* [1] *ApoE* ε4 is associated with a 5 to 20% increased risk for the development of AD. Physiologically *ApoE* binds *APP* and changes the clearance of soluble $A\beta_{1-42}$, whereas pathogenic *ApoE* ε4 allele is showing a reduction on the efficacy of this clearance pathway [1]. Besides that, *in vitro ApoE4* doesn't bind to tau protein what suggests that the protective interaction between the *ApoE* and the tau, which prevent tau phosphorylation and a neurofibrillary tangle formation doesn't happen with the *ApoE* ε4 [3,7-12,14,20].

The mutations of *APP*, *PSEN1,* and *PSEN2* account for 5 to 10% of early-onset AD, while the *ApoE* ε4 allele increases the risk of early and late-onset AD [1-3,6-13,18]. *ApoE* is most commonly expressed as three isoforms: *ApoE*ε2, ε3 and ε4. A single *ApoE ε4* allele represents a 2 to 3-fold increased risk. Two copies of it related to a fivefold or more increase risk. Each inherited *APOE ε4* allele lowers the AD age onset by 6 to 7 years [2,3,9-11]. However this mutation is not sufficient for the AD onset. 40 to 65% of AD patients carry the *ApoE* ε4 allele, but 20 to 25% of the general population also carries one or both *ApoE* ε4 alleles [1].

Recent genetic findings for AD

There are many genes being traced, once they present functional similarities compared to those already known. Most of these genes are related to three pathways: inflammation and immune response, lipid metabolism and intracellular trafficking. Those processes are the triggers for the accumulation of toxic amyloid β protein and the deposition of abnormal hyperphosphorylated tau protein. Some examples of those genes are: *SORL1* gene modulates the intracellular trafficking and processing of APP. *CLU* is a lipoprotein expressed in periphery and the brain. It participates on lipid transportation, like *ApoE*. *CLU* probably influences Aβ-aggregation and receptor-mediated Aβ clearance by endocytosis. *CR1* is part of the complement system (cell-surface receptor), involved in clearing immune-complexes formed by C3b and C4b, is probably involved in Aβ clearance, playing an important role in neuroinflammation process in AD. *ADAM10* is a α-secretase that plays major role in *APP* cleavage. Some of its variants increase Aβ levels *in vitro,* others disrupt α-secretase activity and shift *APP* processing, leading to an amyloidogenic cleavage. *CD2AP* is crucial in receptor-mediated endocytosis. It contributes to *APP* metabolism and subsequent Aβ generation. *BIN1* is involved in membrane trafficking and clathrin (protein that plays a major role in the formation of coated vesicles) mediated endocytosis, what affect *APP* processing and Aβ production/clearance. *PICALM* is related to clathrin-mediated endocytosis. *CD33* inhibits normal functions of immune cells. In the brain it is mainly expressed on microglial cells and is related to the clearance of Aβ mediated by the microglia. *ABCA7* transports many molecules through extra and intracellular membranes. The microglia express high levels of this gene. It also regulates apoptotic cell debris phagocytosis in the brain. *MS4A* downregulates calcium influx, this regulation of calcium signalling plays an important role in neurodegeneration. *TREM2* is a receptor of the innate immune system expressed on microglia, macrophages and dendritic cells, when this receptor is triggered it activates phagocytosis of pathogens and cellular debris. *TREM2* plays an important role on macrophages and microglia suppressing the expression and secretion of inflammatory cytokines. Autosomal recessive mutations lead to dementia cases. *PLD3* is highly expressed in AD affected brain regions and is lower expressed in AD brains neurons. Its overexpression is related to an important decrease in intracellular *APP* and extracellular Aβ42 and Aβ40, once its suppression leads to an increase in extracellular Aβ42 and Aβ40. These findings disclosure the importance of immune response and inflammation in AD pathogenesis [2-4,6,9,10,12,15]. Many genes are already recognized as participants of the pathological mechanisms of AD. However, their action is usually similar or related to the pathways and effects of *APP* and *APOE* as its showed in table 1.

Accumulation of Toxic Amyloid-β Protein and Deposition of Abnormal Hyperphosphorylated Tau-Protein			
Production of Amyloidogenic Substrates		Increased Inflammatory Cytokines or Dysregulation of Phagocytosis	Reduction Clearance of Soluble $A\beta_{1-42}$
Trafficking and Processing of *APP*	Aβ-Production, Clearance and Aggregation	Immune Cells Function	Lipid Transportation
SORL1	*CLU*	*CD33*	*APOE*
BIN1	*BIN1*	*TREM2*	*CLU*
PICALM	*CD33*	*CR1*	
PDL3	*PDL3*	*ABCA7*	
PSEN1	*APP*		
PSEN2	*ADAM10*		
ADAM10			
CD2AP			

Table 1: *Main process related to the AD pathogenesis and the genes related to them.*

Cheng., *et al.* [11] analyzed 68 well-phenotyped Caribbean Hispanic families without clear inheritance patterns, with two or more early-onset cases but lacking mutations in *APP*, *PSEN1*, and *PSEN2*. After studying these families the group disclosure some new genes that are probably related with AD pathogenesis and others that have been related with AD lately (supporting those findings), such as *EPHB2, CR1, RAB10, CDH8, XRCC4, MEF2C, APBB3, EPHA1, PTPN5, FBXL3, DNAJC3, VPS36, CLN3, APOBR, IL4R, ADCY7, FTO, LAMA1, PTPRM, ANKRD12, RAB12, NDUFV2, BCL2, SPTLC3 and NOL4L. EPHB2 is from the* family of receptor tyrosine kinase transmembrane glycoproteins. This gene is probably related with Aβ degradation, once Aβ-derived diffusible ligands interact with *EPHB2* and leads to its degradati-

on. Besides that, EphB2 regulates synaptic localization of N-methyl-D-aspartate (NMDA) receptors. These receptors are associated with NMDAR currents reduction and long-term potentiation impairment. Therefore, increase the *EPHB2 expression in* hippocampus may be an interesting strategy for AD treatment [11]. *RAB10 and RAB12* are members of small GTPases superfamily, which are key regulators of membrane trafficking and crucial for neuronal development. *APBB3* gene encodes a Aβ precursor, A4, which is a member of the protein-binding family B binding to the intracellular domain of the amyloid precursor protein modulating its internalization. *LAMA1* encodes one of the α1 subunits of Laminin, a member of extracellular matrix glycoproteins family, which is an important component of the basal lamina of blood vessels in the central nervous system, supporting the idea that the cerebrovascular dysregulation plays a crucial role in neurodegeneration in AD. *PTPRM* is a member of protein tyrosine phosphatase family, that are signaling molecules, which regulates many cellular processes such as, cell growth, differentiation, and mitotic cycle. *NKRD12* inhibit the transcriptional activity of nuclear receptors. BCL2 are regulators of apoptosis pathways, being associated with neuronal survival regulation. Indeed, the reduction of BCL2 leads to a Aβ-induced neuronal cell death. CLN3 modifies intracellular processing of the amyloid precursor protein. *APOBR* encodes apolipoprotein B receptor, which is associated with endothelial dysfunction and atherothrombogenesis. *CDH8* encodes an adhesion protein that plays an important role in synaptic adhesion and axonal growth and guidance. *PTPN5* gene encodes striatal-enriched protein tyrosine phosphatase, which regulates signaling proteins crucial for synaptic strengthening and NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor trafficking. *DNAJC3 is related with* multisystemic neurodegeneration. *SPTLC3* gene encodes a subunit of serine palmitoyl transferase, which is crucial for regulation of membrane dynamics in the nervous system [11,12]. This study shows the importance of the genetic heterogeneity for AD and how this area can improve the understanding of it as well as tis complex pathogenic process.

Inflammation in AD pathogenesis

The inflammation and immune response are crucial pathways for the AD development. Inflammatory cytokines, the effects played by the macrophages and microglia and the complement system are the most important agents for the inflammation [3,5,8]. The complement classical pathway is related with AD development, once C1q (starter protein in the pathway) enhance Aβ aggregation and fibril formation. Also, others complement proteins, such as C1q, C4 and C3 and the MAC have been found located next to senile plaques and dystrophic neuritis in AD patient's brains. Besides that, mRNA levels of complement proteins are increased those patients. In AD brains the factor B mRNA is present in frontal cortex, and factor D is increased, what shows that Aβ has the potential to activate the alternative pathway. Therefore, the complement system is strongly related with AD pathophysiology, once senile plaques and neurofibrillary tangle related components (without antibodies) could activate this system. This shows that the neurons are a source of complement proteins in the brain [3].

Genes related to image findings, clinical manifestations and CSF findings

Once many people carry the pathogenic gene but don't manifest none symptoms the determination of the pathogenesis of AD is a challenge. Besides that, most patients with neuropathological disease show concomitant diseases, such as cerebrovascular pathology or Lewy body dementia (LBD). To corroborate these findings on image exams only few patients with definite AD show clinical manifestations exclusively associated with AD. There are some unspecific findings on CT and MRI that can help with the AD diagnose, such as cerebral atrophy, which is marked by enlarged ventricles and cortical sulci. The molecular imaging techniques are becoming more important for the AD diagnosis, once the image exams can't deal with it alone. The positron emission tomography (PET) and single photon emission computed tomography (SPECT) are the most used molecular imaging techniques. Two types of PET are being used to diagnose AD, one of them measure brain glucose metabolism (FDG-PET), and the other (amyloid-PET) measures Aβ accumulation in the CNS. Reduced uptake of FDG-PET is indicative of neuronal dysfunction (hypometabolism), what indicates AD. The hypometabolism pattern present with reduced FDG in the parieto-temporal, frontal and posterior cingulate cortices in early AD patients. FDG-PET has high sensitivity and low specificity. Amyloid-PET has a high predictive value, sensitivity, and specificity what can indicate amyloid pathology. $A\beta_{1-42}$ cerebrospinal fluid measures increase with normal aging and overlaps with other dementias. Some genetic modifications are already correlated with image exams findings like the correlation between *ApoEε4* carriers demonstrating accelerated loss of gray matter, increased hippocampal atrophy, increased amyloid deposition, decreased glucose metabolism and increased numbers of cerebral microbleeds, greater medial temporal lobe atrophy; *ApoEε4* non-carriers presented greater frontoparietal atrophy; *BIN1* has been related with entorhinal cortex thickness; *CR1* with brain amyloid burden; *PICALM* with entorhinal cortex thickness and *TOMM40* with volume loss of hippocampal, change of hippocampal gray matter density rate and volumetric variation in various brain regions [1,9,10,16,19].

The cerebrospinal fluid (CSF) can evidence the disease installation, supports some theories about the AD pathogenesis and also correlate some findings with some specific genetic variations. Karch., *et al.* [9] describes some of these changes: There is a strong association between CSF Aβ and *ApoE* genotype. Other genes are also correlated with CSF Aβ levels, such as *SORL1 and CLU*. *ApoE, BIN1*, *PICALM* and *CR1* is also related with CSF tau levels and the gene influences tau levels by Aβ-dependent and Aβ-independent mechanisms [9,10].

Some genes discussed are also related with the disease clinical manifestations evolution. *ApoE* ε4 alleles for example were associated with memory retention impairment. *ApoE* ε4 non-carriers showed greater damage in working memory, executive function, and lexical access. Besides that *APOE* ε4 allele carriers have been showing more recurrent symptoms of depression and have been also associated with increased affective dysregulation rates. Zokaei., *et al.* studied 66 participants with *ApoE ε3/ε3, ε3/ε4* and *ε4/ε4* genotypes, these patients had their short and long-term memory tested. The study disclosed an impaired long-term memory for object locations in *ε4/ε4* carriers and a better short-term memory for object locations in *ε4/ε4* carriers, showing the dissociable effects of *ApoE* variants. Some variants of MS4A are related with reduced rates of affective dysregulation. Variants of BIN1 and EPHA1 are associated with higher rates of abnormal perception and thought contents. The *ApoE* ε2 alleles were related with slower changes in daily functioning and better neuropsychological performance. Therefore, the *ApoE* ε2 is being considered a protective allele. *CR1* gene is related with episodic memory decline [10,14,15,17,19].

Future of genetic in AD

However, the physiopathology of AD and its diagnose still uncertain, what increases the importance of establishing genetic markers for the AD diagnose. The discovery that MicroRNAs (miRNAs) are expressed in the CSF and that miRNAs can affect longevity and stress resistance in several species suggests the possibility that miRNAs may also have important roles in diseases of aging, such as AD. MiRNAs are small, endogenous, non-protein coding RNAs. They are originated from introns or from the transcription of miRNA genes, which are present at different loci in the genome. There are specific miRNAs expressed in CNS, where they are important for the development and aging of the brain, being related with neurodegenerative diseases, like AD. MiRNAs are present at the CSF and blood, so miRNA levels in biofluids can be easily assessed. Therefore, they are being considered as potential biomarkers for the AD diagnosis [1].

Conclusion

Alzheimer's disease (AD) is a neurodegenerative disease and it still incurable. Late-onset Alzheimer disease (AD) is the most frequent form of dementia. The genetic findings of early onset AD are different from the late onset disease. Although cases of familial AD (early onset) present a small prevalence, they can help to identify genetic patterns of the disease, those cases have been associated with autosomal dominant mutations in the genes *PSEN1*, *PSEN2*, and *APP*. The ε4 allele of the apolipoprotein E (*ApoE*) gene is the most known gene linked to late-onset AD. The mutations of *APP*, *PSEN1,* and *PSEN2* account for 5 to 10% of early-onset AD, while the *ApoE* ε4 allele increases the risk of early and late-onset AD. However, this mutation is not sufficient for the AD onset. There are many genes being traced, once they present functional similarities compared to those already known. Most of these genes are related to three pathways: inflammation and immune response, lipid metabolism and intracellular trafficking. Those processes are the triggers for the accumulation of toxic amyloid β protein and the deposition of abnormal hyperphosphorylated tau protein. The inflammation and immune response are crucial pathways for the AD development. Some genetic modifications are already correlated with image exams findings. The cerebrospinal fluid (CSF) can evidence the disease installation, supports some theories about the AD pathogenesis and also correlate some findings with some specific genetic variations. Some genes discussed are also related with the disease clinical manifestations evolution. However, the physiopathology of AD and its diagnose still uncertain, what increases the importance of establishing genetic markers for the AD diagnose, such as the miRNA. In sum the genetic it's probably the most important field to understand the AD development, so studying the genes related to this disease is extremely important to understand the physiopathology involved with the disease and also establishing a treatment, whereas the AD expression is not solely governed by genetic factors.

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