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Genetic Basis of Alzheimer's Disease

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Abstract

Alzheimer's disease, a progressive neurodegenerative and fatal disorder is the most common cause of dementia. It has been reported that 10% of the persons having the age more than 70 years have significant memory loss and more than half of them probably have this disease. This disease generally starts with mild symptoms and ends with a devastating brain damage. The two major neuropathology of this disease include neurotic plaques and neurofibrillary tangles of which the former appears earlier. Depending on the age of onset Alzheimer's disease is categorized into early onset and late onset types. The victims of the early onset form of this disease comprise only 1-6% of the total cases. The major causes of the early onset type of this disease are the mutations mainly in two genes namely-APP and PSEN1. However, mutations in the gene PSEN 2 contribute to some extent also. Although the late onset Alzheimer's disease has a genetic background, it is influenced by other factors, greatest of which is the age. However, recently genome wide association studies has identified some susceptible genes that can contribute also to late onset form of this disease.

Keywords: Stress; Glucocorticoid; Dopamine; Nucleus accumbens; Addiction

Introduction

Dementia is a major neurocognitive disorder characterized by disturbances of major brain function like memory, thinking, ability to learn, language etc. Among the various forms of dementia Alzheimer's disease (AD) is the most common and comprises 60-70% of the cases [1]. AD is a progressive neurodegenerative disease in which the victim dies within 4-8 years from the time of diagnosis [2-4]. The hallmark of pathology of AD includes the formation of extracellular amyloidal plaques and intracellular neurofibrillary tangles (NFT) that cause the loss of neurons and synapses progressively [5]. Plaques are formed by the altered cleavage of a transmembrane protein of neuron and glia called amyloidal precursor protein (APP). On the other hand NFTs are formed by the hyperphophorylation of a microtubule associated protein 'tau' [6]. Depending on the age of onset of the disease, AD can be categorized into two types namely–familial early-onset AD (EOAD) and sporadic late onset AD (LOAD) of which the former includes 1-6% of all patients in the age of 30-60 years. In the later case the age of onset is generally after 65 years [7]. The AD exhibits a complex genetic basis. The familial EOAD arises due to over production of a protein called amyloidal beta (Aβ) due to the mutations in three genes namely- amyloidal precursor protein (APP), presenilin 1(PSEN1) and presenilin 2 (PSEN 2). Familial AD is inherited in a Mendelian dominant fashion without any major environmental influence. In contrast LOAD results from a combination of genetic and environmental factors. The major genetic risk factor is the E4 allele of the apolipoproten E (APOE) [4,8]. In this article we will summarize the influences of mutation of the above mentioned genes in the pathogenesis of AD.

Cellular basis of AD

The extracellular amyloidal plaque and intraneuronal NFT are the two pathological hallmarks of AD [9]. Although neuritic plaques are found in all cases of AD, autopsy studies have exhibited the absence of NFT in many of the mild AD indicating that neurotic plaques are associated with the early symptoms of the AD and NFTs develop in the later course of the disease [10]. Plaques are the extracellular deposits of aggregated Aβ peptides surrounded by dystrophic axons , synaptic terminals as well as processes of astrocytic and microglialcells [11,12]. Neurotoxic Aβ peptides are generated from the sequential proteolysis of a single –pass transmembrane protein APP which is expressed highly in the brain. This protein is believed to play impotant roles in normal brain development and plasticity of adult brain. Aβ is produced in normal individuals but in some cases the molecules aggregate to initiate the disease. It has been posulated that an imbalance in the production and clearance of the 42 amino acid-long form of Aβ i.e. (Aβ42) results In the deposition of the peptide in the senile plaques and instigate a neurotoxic cascade causing symptoms of AD to appear [13,14].

APP undergoes proteolysis in two pathways namely-amyloidogenic and non-amyloidogenic pathways. In non-amyloidogenic pathway, that involves 90% of the APP metabolism, the protein undergoes cleavage by a zinc metalloproteinase called alpha-secretase (α-secretase) whose cleavage site exists in the Aβ region of the APP and generates a harmless, neuroprotective soluble N-terminal fragment (sAPPα) and membrane-bound C-terminal fragment (CTFα). This event

occludes the generation of plaque forming Aβ peptide. CTFα in membrane is later cleared by an enzyme gamma-secretase (γ-secretase) to yield a soluble N-terminal fragment p3 of unknown function and a C-ternimal fragment (AICD) which is left in the membrane. In the amyloidogenic pathway, APP is first cleaved by an enzyme beta- secretase (β-secretase) that does not penetrate the Aβ region of the APP and yields a soluble N-terminal fragment (sAPP) and a C-terminal fragment (CTFβ) that remains bound to the membrane. Since the β-secretase cleavage site remains outside the Aβ region of the APP and more towards the N-terminal end CTFβ is longer than CTFα. Next γ-secretase acts on CTFβ to yield a membrane bound C-terminal fragment (ACID), similar to that is produced in non-amyloidogenic pathway and a N-terminal fragment i.e. Aβ peptide of 38-42 amino acids in the extracellular space, most common of which are Aβ40 and Aβ42. Although Aβ40 is more common but Aβ42 is more fibrillogenic or polymeric and is associated with the disease state [14,15]. Catalytic function of γ-secretase is based on one of its subunits i.e. Presenilin which have 2 homologs – presenelin 1 and presenilin 2. Mutations in these proteins can change the γ-secretase activity increasing the ratio of Aβ [13] NFTs are condensed fibrils made of 'tau' protein arranged in hyperphosphorylated paired helical filaments (PHFs). Normally tau protein promotes the assembly of microtubules that maintains the normal architechture of neuron and assists in intraneuronal transport of proteins and enzyme containing vesicles required for function of cells [16]. However, phosphorylation of tau protein causes the inhibition of microtubule assembly. It has been proposed that excess Aβ deposition leads to intracellular Ca+2 concentartion that causes the activation of calcium-sensitive proteins such as calcium/calmodulin protein kinase (CAMKK2) calcineurin and calpain. Calpain in turn activate the key tau kinases i.e. Glycogen synthase kinase 3 (GSK-3) and cyclin-dependent kinases5(cdk5) that promote tau phosphorylation and tau associated neurodegeneration [17,18] (Figure 1).

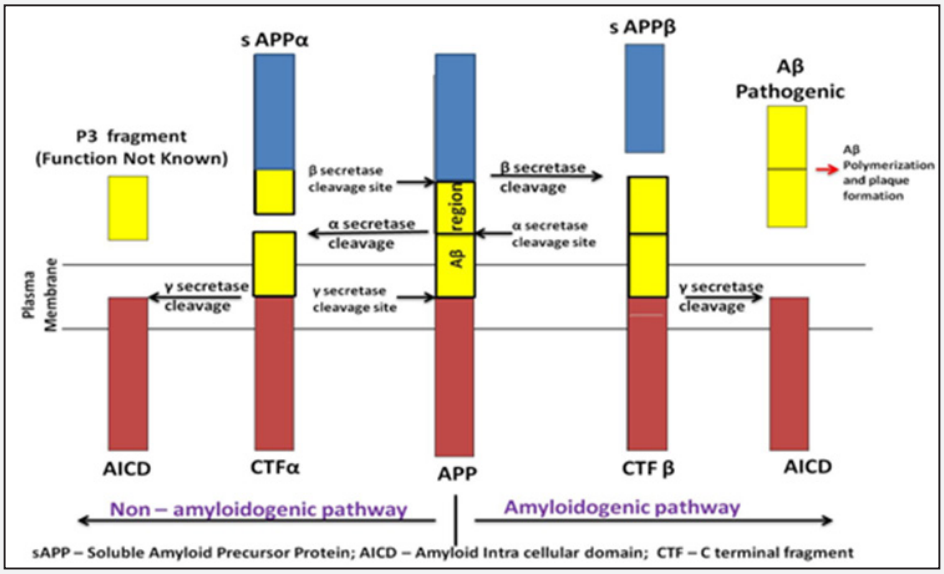

Figure 1: Proceesing of amyloid precurssor protein (APP) in non amylodegenic and amylodegenic pathways.

Genetic Basis of AD

The familial EOAD is inherited in mendelian autosomal dominant fashion and is caused by mutations in three genes namely- APP, PSEN1 and PSEN2. LOAD etiology, on the other hand, is based on the combination of genetic and environmental factors. The epsilon (ε) allele in the apolipoprotein E gene (APOE ε4) has been designated as the genetic determinant of this form of AD. However, some other genes has also been reported to be associated with LOAD. In the following sections, we will discuss the roles of the mutations in these four genes in the etiology of AD.

Mutations in amyloid precursor protein (APP) gene

The APP gene is located on chromosome 21 and has three major isoform namely- APP695(695 amino acids), APP 751(751 amino acids) and APP 770 (770 amino acids). Out of these three isoforms APP 695 is predominantly expressed in neurons [19]. The APP gene contains 19 exons. Thse three isoforms are formed by alternative splicing of the primary APP transcript. APP695 contains exons 1-6, 9-18; APP751 contains exons 1-7, 9-18 and exon 1-18 constitutes the APP 770. It has been demonstrated that the form of APP obtained in plaque correspond to a large protein whose gene was located on chromosome 21. Furthermore, Down syndrome patients who carry an extra copy of chromosome 21 show increased risk of AD in the fifth decade of their lives. All these evidences indicate the involvement of APP gene in AD pathology [4]. More than 30 missense mutations in APP have detected in AD patients [7]. A group of mutations around β-secretase cleavage site have been shown to increase the β-secretase activity directing the APP processing towards amyloidogenic pathway which increases the Aβ load. Mutations near γ-secretase cleavage site increases the Aβ42/40 ratio causing more generation of

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pathogenic Aβ42 [20]. Four missense mutations are reported for codon 717 of APP which is implicated in AD increasing the Aβ42/40 ratio. The amino acid corresponding to this codon lies within the intramembrane region of APP near the γ-secretase cleavage site. The four mutations are V717 F(Indiana), V717 G, V717I (London) and V717L that code for, phenylalanine, glycine, isoleucine and lysine respectively instead of valine [21]. It has been reported that mutations in V717I, V717F and V717G consistently caused a 1.5-1.9 fold increase in the production of longer Aβ42 protein than the Aβ40 and the longer form formed insoluble amyloid fibrils more rapidly than Aβ40. Thus APP 717 mutantions cause AD by generating increased amount of Aβ42 and accelarating amyloid deposition [22].

Mutations in Presenilin 1 and 2 (PSEN1 and PSEN2) genes

γ-secretase is a large complex of integral membrane proteins that performs intermembrane cleavage of a number of membrane proteins including APP and notch [23]. This cleavage is an essential step in various cellular processes. For example, notch signaling is essential for normal maturation and division of hair follicle cells and other types of skin cells. γ-secretase also cleaves APP into several versions of Aβ peptides [24]. Gamma-secretase is composed of four essential subunits-presenilins (PS-1 and PS-2), nicastrin, anterior pharynx defective 1 and presenelin enhancer 2 (PEN-2) [25]. PS is an aspartyl protease, which is the catalytic subunit of γ-secretase. Human PS-1 is a 50kDa transmembrane protein having 467 residues, while its homolog PS-2 is four amino acids shorter that lacks residues 26-29 near the N- terminal end. Both these homologs transverse the membrane 9 times. In the active gamma secretase presenilin is cleaved into two fragments with molecular weight 30kDa (N-terminal) and 20kDa (C- terminal) as a part of transmembrane catalytic event carried out by the same γ-secretase activity that cleaves other substrates. This endoproteolysis of PS remove the steric hindrance-of gamma-secretase caused by cytoplasmic loop between transmembrane domain 6 and 7 enabling it to attain a enzymatically active conformation [26]. The gene for PS-1 and PS-2 are located in chromosome 14 and 1 respectively [27]. Mutations in the PSEN 1 gene that code for PS-1 are the most important cause for FOAD [7,28]. However, the mechanism by which the mutations of PSEN 1 gene cause AD is debated [28]. It has been proposed that PSEN 1 mutations cause the reduction of proteolytic activity of γ-secretase that ultimately increase Aβ 42/40 ratio by impeding sequential cleavage of Aβ peptide. It has also been proposed that, PSEN 1 mutations elevate Aβ42/ Aβ 40 ratio by simply decreasing Aβ 40 level [29]. Mutations in PSEN 1 cause a deleterious gain of function that increase Aβ42 level in brain. It was deduced from the fact that transgenic mice that over expressed mutant PS-1 caused increased Aβ42 than mice over-expressing the wild type version of PS-1 [30]. Mutations in the PSEN 1 have been implicated in 18-50% autosomal dominant cases of EOAD. However, the gene has also been suggested as potential risk gene in LOAD [31]. PSEN 1 mutations show complete penetrance and cause AD onset at the age as early as 30 [7]. For example, it was revealed by the autopsy brains of brother and sister and the archival brain sample of their mother that PSEN 1 gene mutation at amino acid 135 (N135S) caused the onset of AD in them at the age of 30 years [32].

Another PSEN 1 mutation on L134R was detected in a Turkish man with family history of AD who developed symptoms at the age of 53 and died after 4 years later onset of disease [33]. PSEN 1 mutation H163R is a relatively frequent pathogenic mutation found in AD in many population of countries including Europe, Japan, China, Canada, Turkey, USA etc. in which a large number of the victims have shown AD onset age between 40 and 50 years [34]. Apart from these many other familial PSEN 1 mutation such as H 214 Y, L262 V, P264L, A396T, R62H etc. have been detected [35] that comprise only a few of more than 150 PSEN 1 mutations identified till date [7,28]. Contribution of PSEN 2 mutations in EOAD is relatively rare having variable penetrance and has a higher age of disease onset [36,37]. PSEN2 mutation related EOAD is especially found in a very small European population. No report is available regarding PSEN2 in AD patients in Korea, China or japan [37]. Compared to PSEN 1, much fewer missense mutations have been detected in PSEN 2 [4] and similar to PSEN 1 mutations they cause AD by increasing Aβ load [36].

Apolipoprotein E (APOE) gene polymorphism and LOAD

Human APOE is a glycoprotein composed of 299 amino acid and is expressed in several organ, highest being liver followed by brain. In brain it is expressed in nonneuronal tissues mainly in astrocytes and in little amount in microglia. However, at certain conditions neurons can also produce APOE to some extent [38]. It is interesting to note that APOE immune reactivities have been observed in senile plaques and NFT indicating it as the causative factor for LOAD [39]. The APOE gene is located on chromosome 19 and is the only identified gene directly related to LOAD. APOE gene codes for APOE protein which is a cholesterol carrier in the brain. It helps in amyloidal aggregation and the clearance of it. APOE gene exists in the form three polymorphic alleles-APOE ε2, APOE ε3, and APOE ε4 that produce five common genotypes i.e. 2/3, 3/3, 2/4, 3/4 and 4/4. APOE ε2 and APOE ε3 are the common alleles which are harmless. However, APOE ε4 is present in 25-30% of human population and 40% of the victims of LOAD. Although persons harboring APOE ε4 allele do not definitely develop AD but it is regarded as a risk factor gene for this disease. It has been documented that probability of developing LOAD increases 10-fold persons bearing homogygous APOE ε4 than those who are in heterozygous state for this allele [40]. The mechanism by which APOE ε4 allele product promotes the amyloid load is understood. APOE protein contains an N-terminal receptor binding domain and a C-terminal lipid binding domain. Postmortem brain studies have revealed that Aβ has a predilection to be associated more with the C-terminal of the APOE ε4 allele product than the APOE ε3 allele product and the former product undergoes greater N-terminal degradation. This results in more decoration of Aß molecules with APOE ε4

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protein products than APOE ε3 product. It has been proposed that isoform specific differences in the conformation between APOE ε4 and APOE ε3 proteins increase the level of cleavage at the hinge region of APOE ε4. This results in the loss of APOE ε4 functions that mediate the clearance of Aβ, increasing the Aβ load and enhancing the risk of AD in the carriers of APOE ε4 allele in human population [41,42].

Possible Involvement of other genes associated with LOAD

Genome wide association studies (GWAS) have identified some other genes which have the possibility to be associated with LOAD in addition to the contributions made by of APOE ε4 [37,43,44]. For example, Apo lipoprotein J encoded by clusterin gene (CLU) has been identified in amyloidal plaques [43]. Another gene complement receptor 1 (CR1) that codes for C3b complement protein is probably involved in Aβ clearance and mutation in this gene can interfere with Aβ clearance [44] leading to plaque formation. Cadherin-associated protein alpha 3(CTNNA3) gene, located on chromosome 10, encodes a protein called alpha-T catenin can also be involved in LOAD pathogenesis. Seven Polymorphisms in CTNNA3 have shown significant association with LOAD in female patients, who carried the APOE E3 allele [37]. Other genes possibly involved in LOAD pathogenesis are identified as ATP-binding cassette, subfamily A (ABC1), member7 (ABCA7), Bridging integrator1(BIN1), CD2-associated protein(CD2AP), CD33 molecule (CD33), Phosphatidylinositol binding clathrin assembly protein (PICALM) etc [36].

Discussion

Although EOAD contributes a small fraction of total AD cases, it's consequence is very significant as the many patients die before reaching the fifth decade of their lives and even at a lower age. This, no doubt causes enough loses of human resources. Even the LOAD pathogenesis may have a genetic influence contributed by the apoE4 allele. Furthermore genome wide association studies have revealed many susceptible genes whose mutations or polymorphisms can contribute to LOAD. Identification of suitable genetic markers can facilitate the early detection of susceptible person for AD and early medical care can minimize the burden of this disease.

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