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Genetic markers for diagnosis and pathogenesis of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia in the elderly and represents an important and increasing clinical challenge in terms of diagnosis and treatment. Mutations in the genes encoding amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) are responsible for early-onset autosomal dominant AD. The ε4 allele of the apolipoprotein E (APOE) gene has been recognized as a major genetic risk factor for the more common, complex, late-onset AD. Fibrillar deposits by phosphorylated tau are also a key pathological feature of AD. The retromer complex also has been reported to late-onset AD. More recently, genome-wide association studies (GWASs) identified putative novel candidate genes associated with late-onset AD. Lastly, several studies showed that circulating microRNAs (miRNAs) in the cerebrospinal fluid (CSF) and blood serum of AD patients can be used as biomarkers in AD diagnosis. This review addresses the advances and challenges in determining genetic and diagnostic markers for complex AD pathogenesis.

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia in the elderly and leads to death within 3 to 9 years after appearance of symptoms (Isik, 2010). More than 3.5 million people in the world have AD and the ratio of people being diagnosed with AD after 85 years of age exceeds 1 in 3 (Thies et al., 2013). Many molecular lesions have been detected in AD; extracellular amyloid plaques from aggregates of toxic amyloid β (Aβ) and intracellular neurofibrillary tangles composed of hyperphosphorylated tau are the defining lesions in AD (Blennow et al., 2006; Selkoe, 2002). Aβ is composed of 40 or 42 amino acids and is generated through proteolytic cleavage of amyloid precursor protein (APP) (Mawuenyega et al., 2010). Intraneuronal soluble Aβ and amyloid plaques injure synapses and ultimately cause neurodegeneration and dementia leading to AD (Blennow et al., 2006; Hardy and Selkoe, 2002). The toxicity of Aβ appears to be related to the presence of the microtubule-associated protein tau. Endogenous tau blocks Aβ-induced cognitive impairments and the hyperphosphorylated forms of tau aggregate and deposit in AD brains as neurofibrillary tangles (Roberson et al., 2007).

AD is commonly classified into two types based on the time of its onset (Blennow et al., 2006). Early-onset AD, which typically develops before the age 65, is a very rare (<1%) autosomal, dominant, familial disease. This is caused by mutations in the APP and presenilin genes, which are linked to Aβ processing by γ-secretase complexes (Blennow et al., 2006; Hardy and Selkoe, 2002). Late-onset AD, in the majority of AD cases, occurs late in life (>65 years), is sporadic and heterogeneous, and is caused by aging, and genetic and environmental risk factors. Although the causes of late-onset AD pathology are unknown, clearance of Aβ is likely a major contributor to disease development (Mawuenyega et al., 2010). Many family studies and genetic analyses showed that the ε4 allele of the apolipoprotein E (APOE) gene is the major risk factor for late-onset AD (Bu, 2009; Corder et al., 1993; Huang and Mucke, 2012). The human APOE gene exists as three polymorphic alleles consisting of ε2, ε3 and ε4, with a worldwide frequency of 8.4%, 77.9% and 13.7%, respectively (Farrer et al., 1997; Liu et al.,

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid β; Aph-1, anterior pharynx defective 1; AP, adaptor protein; APOE, apolipoprotein E; APP, amyloid precursor protein; AICD, amyloid intracellular domain; BACE-1, β-secretase beta-site amyloid precursor protein-cleaving enzyme 1; BIN1, bridging integrator 1; CLU, clusterin; CNS, central nervous system; CR1, complement component (3b/4b) receptor 1; CSF, cerebrospinal fluid; GWASs, genome-wide association studies; MAPT, microtubule-associated protein tau; miRNAs, microRNAs; OR, odds ratio; PEN2, presenilin enhancer 2; PICALM, phosphatidylinositol binding clathrin assembly protein; pre-MCI, pre-mild cognitive impairment; PSEN1, presenilin 1; PSEN2, presenilin 2; sAPPα, secreted amyloid precursor protein-α; SNPs, single nucleotide polymorphism.

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2013). However, the frequency of the ε4 allele is dramatically increased to approximately 40% in patients with AD (Farrer et al., 1997; Liu et al., 2013).

Many studies on diagnostic markers of AD suggest that circulating biomarkers including Aβ peptides (Aβ40 and Aβ42, which are more prone to aggregation) and tau/phospho-tau (Thr 181, a common phospho-epitope) may be used in AD diagnosis. The genotypic analysis of APOE gene polymorphic alleles is also used as a prognostic marker of late-onset AD. Although studies regarding these diagnostic markers for AD are in progress (Holtzman, 2011; Tarawneh and Holtzman, 2010), large variability and inconsistency exist between studies, delaying the markers' use as a diagnostic tool for AD in the clinical setting (Bertram, 2010; Ingelson et al., 1999). The confirmed genes for AD were well summarized in Table 1 (Alonso Vilatela et al., 2012). A lot of different mutations of them have been reported. However, their potential use as prodromal AD biomarkers remains uncertain. Recently, genome-wide association studies (GWASs) identified putative novel candidate genes, including complement component (3b/4b) receptor 1 (CR1), clusterin (CLU), phosphatidylinositol binding clathrin assembly protein (PICALM) and bridging integrator 1 (BIN1) (Harold et al., 2009; Lambert et al., 2009; Seshadri et al., 2010) and another GWAS showed that common variants in MS4A4/MS4A6E, CD2uAP, CD33 and EPHA1 are also associated with late-onset AD (Naj et al., 2011). In addition, several studies showed that circulating microRNAs (miRNAs) in the cerebrospinal fluid (CSF) and blood serum have characteristic changes in AD patients, suggesting that miRNAs could be used in AD diagnosis, solely or in combination with other AD biomarkers (Dorval et al., 2013).

In this review, we have described the key aspects and research trends related to the use of genetic markers for the diagnosis of AD. GWASs have sought to identify new genetic markers for AD. We have also reviewed an exciting area that has recently received attention, circulating miRNAs as potential genetic and diagnostic markers for AD.

2. APP

Aβ plaques, formed by the deposition and aggregation of extracellular Aβ protein in the brain are the major neuropathological hallmarks of AD. The Aβ was first isolated by Glenner and Wong (2012) from fibrils present in cerebrovascular amyloidosis and in the amyloid plaques associated with AD. Cloning and gene mapping of Aβ revealed that it was synthesized from a larger precursor protein called β-amyloid precursor protein (APP) (Goldgaber et al., 1987). APP is cleaved by two independent proteolytic pathways. The non-amyloidogenic pathway is controlled by α-secretase, which cleaves APP and releases the extracellular amino-terminus of APP as a secreted amyloid precursor protein-α (sAPPα). Next, an 83-residue carboxy-terminal fragment (C83) is digested by γ-secretase, liberating extracellular p3 and the amyloid intracellular domain (AICD). The amyloidogenic pathway combines the sequential actions of β- and γ-secretases, generating Aβ peptides at intracellular sites such as the endoplasmic reticulum and Golgi apparatus (Fig. 1A). The β-secretase, named β-site amyloid precursor protein-cleaving enzyme 1 (BACE-1), cleaves APP, which creates N-terminal sAPPβ and C-terminal C99 peptide. The C99 peptide is cleaved by γ-secretases to generate Aβ, which can misfold and form extracellular fibrils (Bekris et al., 2010), a major component of amyloid plaques found in the AD brain. The most common form of Aβ in humans consists of 40 amino acids (Aβ40), but the long form of Aβ (Aβ42), which has two additional amino acid residues at the C-terminus, was found associated with AD (Iwatsubo et al., 1995; Tandon et al., 2000; Tomiyama et al., 2008). The detail on cleavage sites of APP and substrate specificity of BACE1 were defined by Tomasselli et al. (2003) and summarized in Fig. 1B.

Goate et al. (1991) first reported the segregation of a missense mutation of APP in families with AD and subsequently reported two mutations including a single amino acid substitution (Phe for Val) in the transmembrane domain (Murrell et al., 1991) and a Val for Gly substitution at codon 717 (Chartier-Harlin et al., 1991). Today, more than 30 different APP missense mutations have been identified and approximately 25 of these are pathogenic, in most cases resulting in autosomal dominant early-onset AD (Cruts et al., 2012). Although mutations in APP genes are usually autosomal dominant, the mutation A673V causes AD in an autosomal recessive pattern (Di Fede et al., 2012; Giaccone et al., 2010). Interestingly, the same site mutation A673T showed a strong protective effect against AD. This substitution is adjacent to the aspartyl protease β-site in APP, and results in an approximately 40% reduction in the formation of amyloidogenic peptides in vitro (Jonsson et al., 2012). Copy number variant mutations are also found in APP (Hooli et al., 2012) and Down's syndrome (caused by the presence of an extra chromosome 21) providing three copies of APP. Thus, in these cases, AD is due to an excess of APP (Zekanowski and Wojda, 2009).

3. Presenilin and γ-secretase complexes

Schellenberg et al. (1992) first found evidence of genetic linkage for a familial AD locus on chromosome 14. Subsequently, other groups have mapped a locus (AD3) associated with susceptibility to a very aggressive form of AD to chromosome 14q24.3 by genetic linkage studies. They isolated a minimal co-segregating region containing the AD3 gene and a transcript (S182) corresponding to a novel gene whose product is predicted to contain multiple transmembrane domains and resembles an integral membrane protein. This protein contains five different missense mutations in conserved domains and is highly associated with early-onset familial AD (Sherrington et al., 1995). The protein was named presenilin 1 (PSEN1) and a positional cloning approach identified PSEN1 at 14q24.3 and PSEN2 at 1q31–q42 (Cruts et al., 1996). PSEN1 is a major component of the γ-secretase complex along with nicastrin, anterior pharynx defective 1 (Aph-1), and presenilin enhancer 2 (PEN-2) (Fig. 1). PSEN1 is a polytopic membrane protein that forms the catalytic core of the γ-secretase complex (De Strooper et al., 1998). More than 180 mutations in PSEN1 have been reported (Cruts et al., 2012) and the majority are missense mutations that cause amino acid substitutions. Mutations in PSEN1 are the most common cause of early-onset AD and account for 18–50% of autosomal dominant early-onset AD (Cruts et al., 1996). Mutations in PSEN1 cause the most severe forms of AD with complete penetrance and onset occurring at approximately 58 years of age, but incomplete penetrance has also been reported (Rossor et al., 1996). Many studies have been conducted with various types of PESEN-1 mutations in different ethnic groups. A founder mutation in PSEN1 was reported to cause early-onset AD in unrelated Caribbean Hispanic families (Athan et al., 2001). Yescas et al. (2006) showed that the A431E mutation caused early-onset AD in Mexican families. The PSEN1 L166P mutation was found at an unusual onset

Table 1
Genes associated with Alzheimer's disease.

Gene symbol	Locus	Protein	Inheritance	Age at onset (years)
APP	21q21.2	Amyloid beta A4	Autosomal dominant	40–60
PSEN1	14q24.3	Presenilin-1	Autosomal dominant	30–58
PSEN2	1q31–q42	Presenilin-2	Autosomal dominant	45–88
APOE	19q13.2	Apolipoprotein E	Risk factor	40–90

Alonso Vilatela et al. (2012).

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