Chapter 10

Risk Factors for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common form of dementia in the elderly. Currently there is no effective treatment available. Senile plaques and neurofibrillary tangles are hallmarks of AD pathology, and patients demonstrate cognitive complaints with deficits in various neuropsychological domains. Familial AD (FAD) accounts for 0.5% of all AD cases and usually presents before the age of 65 years. Approximately 50% of the FAD patients carry mutations in one of the following genes: APP, PSEN1, and PSEN2. Inheriting any of these genetic mutations increases $A\beta_{42}$ production, which has been linked to AD pathogenesis. Late-onset AD represents the majority of AD cases, with evidence suggesting impaired Aβ clearance. However, the etiology of late-onset AD is more complex. Several findings suggest that multiple risk genes and factors may contribute to the pathogenesis of LOAD. In this chapter, we elaborate some of these factors and their involvements in the development of AD.

Keywords: Alzheimer's disease, risk genes, risk factors

1. Introduction

Alzheimer's disease (AD) is the most commonly diagnosed dementia in aging individuals older than 65 years [1]. The typical clinical symptoms include progressive cognitive decline and memory impairments. The hallmarks of the disease include aggregation of insoluble Aβ peptides and hyper-phosphorylated tau, resulting in the formation of amyloid plaques and neurofibrillary tangles (NFT), respectively, in the brain. Several studies including sequencing, meta-analysis, and genome-wide association studies have highlighted more than 20 AD-associated loci, as well as several molecular pathways altered in AD pathology.

2. Complexity of the disease

Alzheimer's disease is a complex multifactorial disorder, in which genetic predisposition and environmental factors interact with disease processes. The genetic polymorphism of amyloid precursor protein (APP) or genetic mutations of presenilin 1 (PSEN1) [2] or presenilin 2 (PSEN2) are well known to be the major genetic causes of familial early-onset AD (EOAD) [3–6]. These mutations have been shown to induce a preferential generation of $A\beta_{42}$ with a high propensity for aggregation [7]. On the other hand, the most common genetic risk factor for sporadic AD is the apolipoprotein E (APOE) gene (located on chromosome 19) [8]. Subsequent genome-wide association studies identified several new risk genes [9–11]: the gene for clusterin (CLU) also known as apolipoprotein J (localized on chromosome 8), the gene encoding the complement component (3b/4b) receptor 1 (CR1) (located on chromosome 1), the gene encoding PI-binding clathrin assembly protein (PICALM) (located on chromosome 11), the gene encoding the bridging integrator 1 (BIN1) (located on chromosome 2), and the disabled homolog 1 (DAB1) (located on chromosome 1). Later studies identified additional novel risk loci associated with late-onset AD such as SORL1, TREM2, MS4A, ABCA1 and 7, and CD33 [12]. The implication of these newly identified genes in the disease mechanism(s) are yet to be elucidated, with some evidence suggesting possible involvements in clearance dysfunction, lipid metabolism [13] (El gaamouch et al., 2016 in press), immune response and APP metabolism [14].

Studies conducted on cohorts composed of normal and AD twins not only showed the impact of genetic factors in AD [15], but also revealed a considerable importance of environmental factors in disease onset and development [16]. Environmental factors include socio-demographic factors such as age, level of study, life style, physical activity, eating habits, and tobacco or alcohol consumption. Other comorbidities related to life style such as hypertension, dyslipidemia, and diabetes have also been associated with AD pathogenesis.

In this chapter, we elaborate some of these AD risk genes and environmental factors, as well as their involvements in the pathogenesis of AD based on the state of our current knowledge.

3. Aβ and tau

Aβ isoforms are 39–43 amino acid peptides present as soluble $A\beta_{40}$ or insoluble $A\beta_{42}$. In physiological condition, $A\beta_{40}$ represents more than 90% of Aβ while $A\beta_{42}$ levels are less than 5%. A possible function of Aβ under physiological conditions may be inhibiting γ-secretase activity to generate more Aβ in a negative feedback control mechanism [17]. However, under pathological conditions, $A\beta_{42}$ which is found in high concentrations in AD patients is prone to aggregate lacking the ability to inhibit γ-secretase [18–20].

Aggregated Aβ peptides, either soluble oligomers or fibrils, could induce a cascade of cellular events such as apoptosis [21–24], oxidative injury [24–26], alterations in kinase or phosphatase activities [26–29], microglial activation [30–32], and mitochondrial dysfunction [33–35], which trigger neuronal death [36, 37].

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The role of Aβ in AD pathogenesis has been extensively investigated by a large number of studies. However, only Aβ accumulation is not sufficient to induce AD pathology. AD pathogenesis requires tau protein accumulation and deposits [38, 39]. Some evidence supports the notion that Aβ deposition induces tau pathology by promoting the intra-neuronal formation of NFT which consist of hyper-phosphorylated tau proteins. However, whether Aβ directly interacts with tau aggregates is still under debate [40].

Tau has been identified 40 years ago as a microtubule-associated protein by Weingarten et al [41]. Tau is a highly soluble neuronal protein [42] mainly located in the axons, which promotes microtubule polymerization and stabilization [43]. There are six isoforms expressed in the central nervous system [44]. Under physiological conditions, tau plays an important role in the regulation of axonal transport, neuronal signaling pathways, DNA protection, and synaptic function [45–47]. During early stages of development, tau isoforms are highly phosphorylated [44], and it is hypothesized that fibrillary deposits of hyper-phosphorylated tau contribute to synaptic dysfunction in AD [48].

4. APP, PS, and other genes involved in Aβ biogenesis

As stated above, accumulation and aggregation of Aβ peptide are part of the starting steps of AD. The accumulation can result from Aβ overproduction or an alteration of its clearance. Aβ peptide is derived from APP as a result of sequential cleavage by β- and γ-secretases [49]. Its elimination is mediated through proteolysis and/or lysosome degradation system.

Forty well-known APP gene missense mutations within Aβ coding regions or close to the processing sequence, are shown to result in an increase of Aβ fibril deposition [50, 51] accounting for an autosomal form of the disease: EOAD [52]. Among these mutations, A673V and E693D mutations have been associated to the autosomal recessive EOAD [37, 53], while 30 other dominant mutations were involved in autosomal dominant EOAD [53].

Interestingly, a recent study conducted on the Icelander population highlighted a mutation on APP gene that has a neuroprotective role in AD. It was reported that the A673T mutation of APP, which is close to BACE1 proteolytic site, protects against cognitive loss and AD development in old individuals. They also showed that this mutation reduced levels of $A\beta_{40}$ and $A\beta_{42}$ by approximately 40%. These results were later confirmed by another separate study [54].

APP is subjected to two independent proteolysis [55] known as non-amyloidogenic and amyloidogenic pathways. In non-amyloidogenic pathway, APP is cleaved by α-secretase ADAM within the Aβ amino acid sequence, thus preventing the formation of amyloid peptide fragment [5, 56–58]. ADAM belongs to the disintegrin and metalloproteinase domain protein family [59–61], and ADAM10 is the most represented α-secretase isoform in the brain. A few rare ADAM10 mutations have been associated with LOAD with evidence suggesting that these mutations disrupt α-secretase and increase Aβ deposition [62]. The amyloidogenic pathway is mediated by both β- and γ-secretases to generate Aβ. The γ-secretase, which catalyzes APP cleavage into toxic Aβ fragments, is formed by a complex formation of four components: PSEN1, PSEN2, nicastrin, APH-1, and PEN2 [53].

While APP mutations account for a small part of EOAD, mutations on PSEN1/PSEN2 have been identified as critical genes in EOAD [63], which are shown to increase $A\beta_{42}/A\beta_{40}$ ratios and promote $A\beta_{42}$ accumulation [64, 65]. After proteolytic cleavage of full-length presenilin to generate N-terminal and C-terminal fragments and assembly into γ-secretase complex, γ-secretase is transported to cell surface where it acts on APP processing and cleavage. Both PSEN1 and 2 mutations increase formation of Aβ species and deposition of amyloid plaques [63, 66, 67]. PSEN1 mutations by altering APP γ-secretase cleavage site promote $A\beta_{42}$ generation [68]. PSEN2 mutations lead to AD with a slower progression than PSEN1 mutations [67].

Besides their role in APP processing, presenilins are involved in many other cellular functions such as Notch signaling and differentiation [69], calcium homeostasis [70], gene expression via interaction with transcriptional coactivators like CREB-binding protein [71]. It was reported that PSEN1 exhibited neuroprotective functions through ephrin-B [72], and that defects in these functions with genetic modifications are implicated in AD pathogenesis. In AD transgenic animal models, APP mutations or in combination with presenilin 1 mutations induced Aβ plaque formation similarly to what were seen in AD human brains [73]. Interestingly, comparatively to sporadic AD cases, patients with PSEN1 mutations had more senile plaques and NFTs developed in their brains, suggesting that PSEN1 may enhance tau deposition as well [74].

5. Genetic risk factors in sporadic AD

Among all identified genetic factors involved in the disease, APOE gene has been extensively studied over the past decade or so. APOE is a major risk gene associated with AD, is located on chromosome 19 [75], and encodes for apolipoprotein E, a 34-kDa lipid binding protein involved in triglycerides and cholesterol transport [76–81]. Three ApoE isoforms which differ by single amino acid substitutions have been found in humans: ApoE2, ApoE3, and ApoE4. ApoE4 carriers present with high levels of cholesterol and LDL in the plasma, which predispose the carriers to cardiovascular disease and AD [82]. ApoE4 carriers contribute to about 50% of AD cases. While ApoE2 decreases the risk and delays the onset of AD [53], ApoE4 multiplies the risk of EOAD and late-onset AD (LOAD) by approximately 3-fold for heterozygous and 10-fold for homozygous carriers [62]. ApoE4 is shown to increase amyloid plaque formation by altering Aβ clearance [83] and promoting fibrillary aggregations [84].

New methods of genetic mapping of single-nucleotide polymorphisms (SNP) provided new information regarding genes involved in increasing or decreasing the risk of AD. Besides well-established AD risk genes described above, nine additional AD-related genes including complement receptor 1 (CR1), bridging integrator 1 (BIN1), clusterin (CLU), phosphatidylinositol-binding clathrin assembly protein (PICALM), MS4A4/MS4A6E, CD2AP, CD33, EPHA1, and ATP-binding cassette transporter (ABCA7) have been unveiled by genome-wide association and sequencing studies [85, 86].

The CR1 gene polymorphism rs6656401 was the first found to be associated with AD in European population [85]. A study conducted on two Canadian cohorts further showed that

polymorphisms in CR1 (rs6656401 and rs3818361), BIN1 (rs7561528), and CD33 (rs3865444) are highly associated with LOAD [87]. The CD33 polymorphism seems to provide neuroprotection against AD through inhibition of CD33 expression with a subsequent decrease in brain $A\beta_{42}$ levels [88].

Recent studies have also identified a risk gene: the triggering receptor expressed on myeloid cells 2 (TREM2) encodes an immune receptor preferentially expressed in microglia, which are involved in inflammation and phagocytosis [89–91]. TREM2 is localized in cerebral regions where AD pathologies exhibit [90, 92, 93]. Some evidence suggests that activated TREM2 is involved in Aβ clearance during AD [94, 95]. A study reported that TREM2 mutations prevent its physiological function in Aβ clearance [90]. Autosomal recessive loss-of-function mutations of TREM2 are associated with increased risks of AD leading to development of early-onset dementia [96].

TREM2 receptor is found to be cleaved in the ectodomain to release a soluble fragment (sTREM2) that is detectable in cerebrospinal fluid (CSF) [96, 97]. A cross-sectional study reported that sTREM2 levels in the CSF of AD patients were higher than in controls while TREM2 variant (R136Q, D87N, Q33X, or T66M) carriers exhibited lower levels of CSF sTREM2. Interestingly, R47H variant carriers displayed significantly higher levels of CSF sTREM2 than non-carriers, suggesting that this variant different from other variants, increases AD risk through a mechanism not necessarily involving TREM2 protein expression. This study also showed that elevated sTREM2 levels in the CSF were strongly correlated with levels of tau and hyper-phosphorylated tau but not with $A\beta_{42}$ levels [96, 98]. These observations have been reproduced by another study [97], implicating that elevated CSF sTREM2 levels could be used as a potential biomarker for early symptomatic phase of AD.

ATP-binding cassette subfamily B member (ABCB) gene has been reported to play a role in AD pathogenesis as well. ABCB encodes P-glycoprotein (P-gp) which is essential for Aβ clearance, and its inhibition as a consequence of genetic polymorphisms prevented Aβ clearance in an AD mouse model [99]. Decrease in P-gp expression levels was found to correlate with increased Aβ deposition [100].

Finally, a recent meta-analysis in combination with sequencing study identified five novel genes associated with AD: HLA-DRB5–HLA-DRB1, PTK2B, SORL1, SLC24A4-RIN3, and DSG2 [101]. Their functional roles in disease mechanisms are yet to be characterized.

6. Epigenetic alterations in AD

Epigenetic variabilities such as histone modifications, DNA methylation/demethylation, and microRNA regulation have been reported not only in the aging processes of different tissues but also in neurodegenerative diseases such as AD. These epigenetic changes might play a pathogenic role in disease mechanism [102–108].

6.1. Histone modifications

A few recent studies reported histone modifications in AD [105, 109, 110]. For example, histone acetylation such as H4 acetylation was decreased in APP/PS1 transgenic mice, which might be involved in cognitive deficits [109, 111, 112]. Another study reported increased H3 and H4 acetylation in the 3xTg-AD mouse model compared to wild-type mice [113]. Levels of phosphorylated histone proteins such as HDAC6 and H3S10 were found to be increased in AD brain regions and neurons [114, 115]. Finally, levels of methylation, acetylation, and phosphorylation of histone H3 were showed to be elevated in AD individual cortex [116].

6.2. DNA methylation/demethylation

Genes containing CpG islands are methylated in their promoter regions. Differences in methylation have been reported in APP, BACE, PS1, and APOE genes [105, 107]. For example, one study showed that methylation in APP promoter region was decreased in the brains of old AD patients compared to young [117]. Evidence suggests that hypo-methylated promoter region of APP gene was correlated with an increased Aβ production [118], which resulted in an increase of the genome-wide hypo-methylation, leading to upregulation of neuro-inflammation and apoptosis genes, subsequently applying a positive feedback control on Aβ production [105].

The changes in DNA methylation at PSEN1 and APOE promoter regions are variable based on results from different studies. PSEN1 promoter may be up- or downregulated by DNA methylation in AD [119, 120]. PSEN1 promoter hypo-methylation increased PSEN1 expression which resulted in an elevated Aβ production [121]. The APOE gene presents a duality in its structure; while its 5′-promoter CpG site is hypo-methylated, the 3′-CpG island is hyper-methylated. Wang et al. suggested that aberrant epigenetic modifications in these CpG sites may contribute to LOAD [105, 118]. High levels of CLU (APOJ) gene, due to high methylation of CpG regions in the promoter of CLU, were observed in AD and might be associated with disease severity and clinical progression [122].

Tau promoter region was also found to be affected by methylation changes during AD [117]. For example, $A\beta_{25–35}$ induced demethylation and increased tau phosphorylation and NFTs formation [123], which may be resulted from hypo-methylation of protein phosphatase 2A (PP2A) [102, 103, 124].

Recently, Sánchez-Mut et al. studied CpG 5′-region gene methylation patterns in different brain regions of AD mouse models and found hyper-methylation of three new target genes which could be involved in AD: thromboxane A2 receptor (TBXA2R), sorbin and SH3 domain containing 3 (SORBS3), and spectrin β4 (SPTBN4) [125]. Finally, genes involved in cell cycle and apoptosis were found to be modulated by DNA methylation and upregulated in AD neurons and aging AD brains [105].

6.3. miRNAs regulation in AD

MicroRNAs (miRNAs) are noncoding regulatory RNAs that are known to modulate ~60% of genome via post-transcriptional gene silencing. The alterations in epigenetic modulations by

miRNAs may promote abnormal expression of genes involved in AD [126, 127]. For example, Kumar et al. discovered a unique signature of seven circulating miRNAs in the plasma that could differentiate AD from non-AD individuals with >95% accuracy [128]. Similarly, another miRNA-based signature from blood samples has been reported, which allowed disease detection with 93% accuracy and 95% specificity [129]. It was also reported that four miRNAs (miRNA-9, miRNA-125b, miRNA-146a, miRNA-155) were involved in pathogenic signaling in AD brains and increased levels of these miRNAs were found in the CSF and brain samples of AD patients [130].

Within an exhausted list of miRNAs in AD pathogenesis, some directly regulate APP mRNA [105]. For example, miR-101 subexpression decreased APP levels and Aβ plaque formation in neurons [131]. Conversely, miR-16 over-expression may trigger an impaired APP expression [132]. miR-124 was reported to alter splicing of APP exons 7 and 8 in neurons [133], and to regulate BACE1 expression [112]. Over-expression of miR-29c, miR-298, miR-328, and miR-195 reduced BACE1 expression and thereby decreased Aβ generation [134–136].

Several miRNAs were found to regulate tau expression. For example, miR-132 was downregulated in some tauopathies [133]. miR-9, miR-124, and miR-15a were reported to be downregulated in AD, affecting tau levels [78, 133]. The miR-15/ERK1 pathway that modulates tau hyper-phosphorylation was found to be downregulated in AD brains [78]. Altered levels of miR-26a in AD inhibited GSK-3β expression and thus affected production of NFT and Aβ in AD [137–139]. In a mouse model with impaired miRNA production, tau was highly phosphorylated leading to NFT formation in mouse brains [140]. Finally, downregulation of miR-212 was involved in NFT density in AD [139, 141].

7. Gender differences

Sex difference has a strong impact on AD risk. More than 60% of AD individuals are composed of postmenopausal women [76, 77]. Two decades ago, a study showed that APOE4 risk for AD was higher in women. Women expressing just one allele of APOE4 presented the same risk to develop AD as men with two APOE4 alleles [142]. This observation has been confirmed by other studies [142–145]. APOE4 women with a single allele had a fourfold increase in risks of having AD, similarly as men with two copies of APOE4 allele [143]. APOE4 homozygous women exhibited the greatest risk of developing AD and the shortest age of onset when compared to APOE2 or 3 carriers [142, 143, 145]. The gender effects on rate of cognitive decline were also reported in APOE4 female carriers compared to men. For example, APOE4 heterozygous women displayed a faster decline in cognitive deterioration than elderly heterozygous men [142]. Compared to men, APOE4 female carriers presented with a reduced neuronal network connectivity in the anterior cingulate cortex which is structurally connected to medial temporal lobe, showing reduced glucose metabolism [146]. Payami et al. showed that APOE4 female mild cognitive impairment (MCI) patients displayed higher levels of CSF tau/Aβ ratios and tau than male MCI carriers [143]. APOE4 female carriers suffering from mild AD were more prone to have high burden of Aβ plaques and NFT than AD male carriers [147].

Finally, estrogen receptor (ER) has been shown to regulate the risk of AD [80, 148]. Two ERs are involved in this regulation: ERα and β. While ERβ was found to downregulate APOE gene and protein expression, ERα acted on upregulation of APOE expression. Genetic polymorphisms in both ER (rs4986938) and (rs2234693) have been associated with high risks of AD [148].

8. Environmental factors

Cohort studies have shown that educational levels play a critical role in neurodegenerative diseases. A lower education level was found to be associated with a higher risk of developing dementia [149–151]. Based on the hypothesis of cerebral cognitive reserve, intellectual training as indicated by educational levels could contribute to the development of neural networks through densification of synapses and increase of brain vascularization [152]. Intellectual solicitation could then maintain dense networks in working conditions according to "Use it or Lose it" principle. Besides levels of knowledge acquired during youth, intellectual stimulation as frequent practice of intellectual activities in adulthood [153] and older ages [154] appears to be associated with a lower risk of dementia.

Lifestyle has an impact on the risk to develop AD as well. Longitudinal studies conducted in Europe and USA demonstrated positive effects of wealth activities such as social, physical, and intellectual activities on decreased risks of AD [155]. Recent longitudinal studies conducted in general population reported an association of regular practice and/or sustained physical activities with lower risks of cognitive decline and dementia [156–160].

Vascular diseases are precipitating factors for AD. The relationship between blood pressure and dementia is complex [161]. Some epidemiological studies suggest that depending on the period of life hypertension appeared (before or after age of 65), high blood pressure did not exhibit homogeneous effects on the risk of dementia. For example, untreated hypertension around age of 50 increased the risk of developing dementia by four-fold compared to individuals with normal blood pressure [162].

Cholesterol, as an essential component of the brain, plays a critical role in regulation of amyloid plaque formation. However, results from numerous studies of the relationship between cholesterol levels and AD were rather contradictory [163]. Some studies showed that high levels of cholesterol were found to increase risks of dementia by two-fold. This hypothesis led to clinical trials testing the use of statins which lower cholesterol production as treatment of AD. Besides cholesterol, hyperglycemia affects the risks of developing vascular dementia and AD. The risk of dementia was increased by up to three-fold among individuals with diabetes [164].

Finally, the effect of nutrition on AD becomes a growing interest in recent years [164, 165]. Food intake plays a decisive role in the onset of systemic diseases such as hypertension, hyperlipidemia, diabetes, and cardiovascular disease which are closely associated to the risk of AD. Several cohort studies showed a relationship between antioxidant intake and lower

risks of dementia and cognitive decline. Aging studies conducted in Europe demonstrated protective roles of fish consumption, which is rich in omega 3 polyunsaturated fatty acids (PUFA). The risk of cognitive decline was decreased in individuals displaying high omega 3 PUFA levels [166–168]. Interactions between fat dietary intake and genetic characteristics (including genes involved in lipid metabolism and transport) are implicated in this phenomenon. For example, similar dietary intakes did not exhibit the same effects on cognitive function in individuals with different genetic heritage. Moreover, conflicted observations were reported from longitudinal studies of the association between nutrient involved in the cycle of homocysteine (including vitamins B6, B12, and folate) and the risk of dementia and/or cognitive deficit.

9. Conclusion

It is clear that Alzheimer's disease (AD) that affects a growing number of individuals is a complex disease endowed with different facets. In this chapter, we summarize the state of knowledge in matters of research on AD based on studies that have contributed to major discoveries in the field. We provide a global overview about current understanding of the disease.

As we enunciated it above, there is a strong genetic predisposition to AD. Mutations and polymorphism in key genes such as APP, PSEN, and APOE affect different aspects of disease pathogenesis such as accumulation of aggregating proteins, defective clearance mechanism, lipid dyshomeostasis, neuronal dysfunction, and synaptic dysfunction. Environmental factors, which most of the time during evolution are responsible for genetic mutations, interact with genetic risk factors and contribute to AD development. Gender difference also has a considerable impact on the apparition of AD.

The complexity and multiplicity of these risk factors make AD an extremely difficult disease to treat. In fact, as of today, even if we have a better knowledge regarding some of these factors, researchers continue to discover new players. These findings raise the question of whether these factors are linked together, which ones are causes or consequences of the disease, how do they act: independently, or in an event cascade starting from a unique triggering factor. Many therapeutic approaches aimed at reducing clinical symptoms or preventing the disease have been developed and tested in clinical trials over the years. However, we have to acknowledge the fact that before we establish the cause and effect link between all these risk factors, and possibly provide a case-by-case treatment of the disease to individuals, it may be difficult to establish an effective treatment based on the heterogeneity of AD individuals.

10. Methods

Article research was performed using Pubmed database and key words such as Alzheimer's disease, environmental factors, and genes were used for database search of articles published

from 1975 to 2016. Articles relevant for the review were selected based on different criteria such as topics of interests, scientific rigor, and reproducibility of results.

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