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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 $A\beta$ 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 $A\beta$ 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. $A\beta$ and tau

$A\beta$ 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 $A\beta$ while $A\beta_{42}$ levels are less than 5%. A possible function of $A\beta$ under physiological conditions may be inhibiting γ -secretase activity to generate more $A\beta$ 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 $A\beta$ 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].

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

As stated above, accumulation and aggregation of A β peptide are part of the starting steps of AD. The accumulation can result from A β overproduction or an alteration of its clearance. A β 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 A β coding regions or close to the processing sequence, are shown to result in an increase of A β 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 Icelandic 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 β_{40} and A β_{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 A β 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 A β deposition [62]. The amyloidogenic pathway is mediated by both β - and γ -secretases to generate A β . The γ -secretase, which catalyzes APP cleavage into toxic A β 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 $A\beta$ 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 $A\beta$ 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 $A\beta$ 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 β_{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 A β clearance during AD [94, 95]. A study reported that TREM2 mutations prevent its physiological function in A β 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 β_{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 A β clearance, and its inhibition as a consequence of genetic polymorphisms prevented A β clearance in an AD mouse model [99]. Decrease in P-gp expression levels was found to correlate with increased A β 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 A β 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 A β 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 A β 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 β_{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 β 4 (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 A β 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 A β 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-3 β expression and thus affected production of NFT and A β 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/A β ratios and tau than male MCI carriers [143]. APOE4 female carriers suffering from mild AD were more prone to have high burden of A β 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: ER α and β . While ER β was found to downregulate APOE gene and protein expression, ER α 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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References

- [1] Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, et al. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry*. 2006;63(2):168–74.
- [2] Sobhanifar S, Schneider B, Lohr F, Gottstein D, Ikeya T, Mlynarczyk K, et al. Structural investigation of the C-terminal catalytic fragment of presenilin 1. *Proc Natl Acad Sci U S A*. 2010;107(21):9644–9.
- [3] Chartier-Harlin MC, Crawford F, Houlden H, Warren A, Hughes D, Fidani L, et al. Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. *Nature*. 1991;353(6347):844–6.
- [4] Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*. 1991;349(6311):704–6.

- [5] Gandy S, Caporaso G, Buxbaum J, Frangione B, Greengard P. APP processing, A beta-amyloidogenesis, and the pathogenesis of Alzheimer's disease. *Neurobiol Aging*. 1994;15(2):253–6.
- [6] Sahlin C, Lord A, Magnusson K, Englund H, Almeida CG, Greengard P, et al. The Arctic Alzheimer mutation favors intracellular amyloid-beta production by making amyloid precursor protein less available to alpha-secretase. *J Neurochem*. 2007;101(3):854–62.
- [7] Bekris LM, Yu CE, Bird TD, Tsuang DW. Genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol*. 2010;23(4):213–27.
- [8] Lambert JC, Amouyel P. Genetic heterogeneity of Alzheimer's disease: complexity and advances. *Psychoneuroendocrinology*. 2007;32(Suppl 1):S62–70.
- [9] Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet*. 2009;41(10):1094–9.
- [10] Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. 2009;41(10):1088–93.
- [11] Hu X, Pickering E, Liu YC, Hall S, Fournier H, Katz E, et al. Meta-analysis for genome-wide association study identifies multiple variants at the BIN1 locus associated with late-onset Alzheimer's disease. *PLoS One*. 2011;6(2):e16616.
- [12] Allen M, Zou F, Chai HS, Younkin CS, Crook J, Pankratz VS, et al. Novel late-onset Alzheimer disease loci variants associate with brain gene expression. *Neurology*. 2012;79(3):221–8.
- [13] Zhu L, Zhong M, Elder GA, Sano M, Holtzman DM, Gandy S, et al. Phospholipid dysregulation contributes to ApoE4-associated cognitive deficits in Alzheimer's disease pathogenesis. *Proc Natl Acad Sci U S A*. 2015;112(38):11965–70.
- [14] De Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell*. 2016;164(4):603–15.
- [15] Gatz M, Mortimer JA, Fratiglioni L, Johansson B, Berg S, Reynolds CA, et al. Potentially modifiable risk factors for dementia in identical twins. *Alzheimers Dement*. 2006;2(2):110–7.
- [16] Bird TD. Genetic factors in Alzheimer's disease. *N Engl J Med*. 2005;352(9):862–4.
- [17] Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, et al. APP processing and synaptic function. *Neuron*. 2003;37(6):925–37.
- [18] Burdick D, Soreghan B, Kwon M, Kosmoski J, Knauer M, Henschen A, et al. Assembly and aggregation properties of synthetic Alzheimer's A4/beta amyloid peptide analogs. *J Biol Chem*. 1992;267(1):546–54.

- [19] Gravina SA, Ho L, Eckman CB, Long KE, Otvos L, Jr., Younkin LH, et al. Amyloid beta protein (A beta) in Alzheimer's disease brain. Biochemical and immunocytochemical analysis with antibodies specific for forms ending at A beta 40 or A beta 42(43). *J Biol Chem.* 1995;270(13):7013–6.
- [20] Kim J, Kleizen B, Choy R, Thinakaran G, Sisodia SS, Schekman RW. Biogenesis of gamma-secretase early in the secretory pathway. *J Cell Biol.* 2007;179(5):951–63.
- [21] Small DH, Mok SS, Bornstein JC. Alzheimer's disease and Abeta toxicity: from top to bottom. *Nat Rev Neurosci.* 2001;2(8):595–8.
- [22] Morishima Y, Gotoh Y, Zieg J, Barrett T, Takano H, Flavell R, et al. Beta-amyloid induces neuronal apoptosis via a mechanism that involves the c-Jun N-terminal kinase pathway and the induction of Fas ligand. *J Neurosci.* 2001;21(19):7551–60.
- [23] Roth KA. Caspases, apoptosis, and Alzheimer disease: causation, correlation, and confusion. *J Neuropathol Exp Neurol.* 2001;60(9):829–38.
- [24] Zhu N, Lin J, Wang K, Wei M, Chen Q, Wang Y. Huperzine A protects neural stem cells against Abeta-induced apoptosis in a neural stem cells and microglia co-culture system. *Int J Clin Exp Pathol.* 2015;8(6):6425–33.
- [25] Yatin SM, Varadarajan S, Link CD, Butterfield DA. In vitro and in vivo oxidative stress associated with Alzheimer's amyloid beta-peptide (1–42). *Neurobiol Aging.* 1999;20(3):325–30; discussion 39–42.
- [26] Varadarajan S, Yatin S, Aksenova M, Butterfield DA. Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. *J Struct Biol.* 2000;130(2–3):184–208.
- [27] Mark RJ, Hensley K, Butterfield DA, Mattson MP. Amyloid beta-peptide impairs ion-motive ATPase activities: evidence for a role in loss of neuronal Ca²⁺ homeostasis and cell death. *J Neurosci.* 1995;15(9):6239–49.
- [28] Ezeani M, Omabe M. A new perspective of lysosomal cation channel-dependent homeostasis in Alzheimer's disease. *Mol Neurobiol.* 2016;53(3):1672–8.
- [29] Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* 2015;14(4):388–405.
- [30] Weggen S, Eriksen JL, Das P, Sagi SA, Wang R, Pietrzik CU, et al. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. *Nature.* 2001;414(6860):212–6.
- [31] Neniskyte U, Neher JJ, Brown GC. Neuronal death induced by nanomolar amyloid beta is mediated by primary phagocytosis of neurons by microglia. *J Biol Chem.* 2011;286(46):39904–13.

- [32] Liu S, Liu Y, Hao W, Wolf L, Kiliaan AJ, Penke B, et al. TLR2 is a primary receptor for Alzheimer's amyloid beta peptide to trigger neuroinflammatory activation. *J Immunol.* 2012;188(3):1098–107.
- [33] Anandatheerthavarada HK, Biswas G, Robin MA, Avadhani NG. Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. *J Cell Biol.* 2003;161(1):41–54.
- [34] Devi L, Prabhu BM, Galati DF, Avadhani NG, Anandatheerthavarada HK. Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. *J Neurosci.* 2006;26(35):9057–68.
- [35] Barsoum MJ, Yuan H, Gerencser AA, Liot G, Kushnareva Y, Graber S, et al. Nitric oxide-induced mitochondrial fission is regulated by dynamin-related GTPases in neurons. *EMBO J.* 2006;25(16):3900–11.
- [36] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science.* 2002;297(5580):353–6.
- [37] Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. *Nature.* 2002;416(6880):535–9.
- [38] Le MN, Kim W, Lee S, McKee AC, Hall GF. Multiple mechanisms of extracellular tau spreading in a non-transgenic tauopathy model. *Am J Neurodegener Dis.* 2012;1(3):316–33.
- [39] Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. *Physiol Rev.* 2004;84(2):361–84.
- [40] Musiek ES, Holtzman DM. Three dimensions of the amyloid hypothesis: time, space and 'wingmen'. *Nat Neurosci.* 2015;18(6):800–6.
- [41] Weingarten MD, Lockwood AH, Hwo SY, Kirschner MW. A protein factor essential for microtubule assembly. *Proc Natl Acad Sci U S A.* 1975;72(5):1858–62.
- [42] Trojanowski JQ, Schuck T, Schmidt ML, Lee VM. Distribution of tau proteins in the normal human central and peripheral nervous system. *J Histochem Cytochem.* 1989;37(2):209–15.
- [43] Gotz J, Xia D, Leinenga G, Chew YL, Nicholas H. What renders TAU toxic. *Front Neurol.* 2013;4:72.
- [44] Goedert M, Spillantini MG, Jakes R, Rutherford D, Crowther RA. Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron.* 1989;3(4):519–26.
- [45] Sultan A, Nessler F, Violet M, Begard S, Loyens A, Talahari S, et al. Nuclear tau, a key player in neuronal DNA protection. *J Biol Chem.* 2011;286(6):4566–75.

- [46] Pooler AM, Usardi A, Evans CJ, Philpott KL, Noble W, Hanger DP. Dynamic association of tau with neuronal membranes is regulated by phosphorylation. *Neurobiol Aging*. 2012;33(2):431 e27–38.
- [47] Mondragon-Rodriguez S, Trillaud-Doppia E, Dudilot A, Bourgeois C, Lauzon M, Leclerc N, et al. Interaction of endogenous tau protein with synaptic proteins is regulated by N-methyl-D-aspartate receptor-dependent tau phosphorylation. *J Biol Chem*. 2012;287(38):32040–53.
- [48] Frandemiche ML, De Seranno S, Rush T, Borel E, Elie A, Arnal I, et al. Activity-dependent tau protein translocation to excitatory synapse is disrupted by exposure to amyloid-beta oligomers. *J Neurosci*. 2014;34(17):6084–97.
- [49] Bettens K, Sleegers K, Van Broeckhoven C. Current status on Alzheimer disease molecular genetics: from past, to present, to future. *Hum Mol Genet*. 2010;19(R1):R4–R11.
- [50] Citron M, Oltersdorf T, Haass C, McConlogue L, Hung AY, Seubert P, et al. Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. *Nature*. 1992;360(6405):672–4.
- [51] Di Fede G, Catania M, Morbin M, Rossi G, Suardi S, Mazzoleni G, et al. A recessive mutation in the APP gene with dominant-negative effect on amyloidogenesis. *Science*. 2009;323(5920):1473–7.
- [52] Kutoku Y, Ohsawa Y, Kuwano R, Ikeuchi T, Inoue H, Ataka S, et al. A second pedigree with amyloid-less familial Alzheimer's disease harboring an identical mutation in the amyloid precursor protein gene (E693delta). *Intern Med*. 2015;54(2):205–8.
- [53] Guerreiro RJ, Gustafson DR, Hardy J. The genetic architecture of Alzheimer's disease: beyond APP, PSENs and APOE. *Neurobiol Aging*. 2012;33(3):437–56.
- [54] Kokawa A, Ishihara S, Fujiwara H, Nobuhara M, Iwata M, Ihara Y, et al. The A673T mutation in the amyloid precursor protein reduces the production of beta-amyloid protein from its beta-carboxyl terminal fragment in cells. *Acta Neuropathol Commun*. 2015;3:66.
- [55] Bohm C, Chen F, Sevalle J, Qamar S, Dodd R, Li Y, et al. Current and future implications of basic and translational research on amyloid-beta peptide production and removal pathways. *Mol Cell Neurosci*. 2015;66(Pt A):3–11.
- [56] Ray B, Long JM, Sokol DK, Lahiri DK. Increased secreted amyloid precursor protein-alpha (sAPPalpha) in severe autism: proposal of a specific, anabolic pathway and putative biomarker. *PLoS One*. 2011;6(6):e20405.
- [57] Sahlin C, Pettersson FE, Nilsson LN, Lannfelt L, Johansson AS. Docosahexaenoic acid stimulates non-amyloidogenic APP processing resulting in reduced Abeta levels in cellular models of Alzheimer's disease. *Eur J Neurosci*. 2007;26(4):882–9.

- [58] Thinakaran G, Koo EH. Amyloid precursor protein trafficking, processing, and function. *J Biol Chem*. 2008;283(44):29615–9.
- [59] Asai M, Hattori C, Szabo B, Sasagawa N, Maruyama K, Tanuma S, et al. Putative function of ADAM9, ADAM10, and ADAM17 as APP alpha-secretase. *Biochem Biophys Res Commun*. 2003;301(1):231–5.
- [60] Fahrenholz F, Gilbert S, Kojro E, Lammich S, Postina R. Alpha-secretase activity of the disintegrin metalloprotease ADAM 10. Influences of domain structure. *Ann N Y Acad Sci*. 2000;920:215–22.
- [61] Fuwa H, Takahashi Y, Konno Y, Watanabe N, Miyashita H, Sasaki M, et al. Divergent synthesis of multifunctional molecular probes to elucidate the enzyme specificity of dipeptidic gamma-secretase inhibitors. *ACS Chem Biol*. 2007;2(6):408–18.
- [62] Suh J, Choi SH, Romano DM, Gannon MA, Lesinski AN, Kim DY, et al. ADAM10 missense mutations potentiate beta-amyloid accumulation by impairing prodomain chaperone function. *Neuron*. 2013;80(2):385–401.
- [63] Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature*. 1995;375(6534):754–60.
- [64] Bergmans BA, De Strooper B. gamma-secretases: from cell biology to therapeutic strategies. *Lancet Neurol*. 2010;9(2):215–26.
- [65] Chavez-Gutierrez L, Bammens L, Benilova I, Vandersteen A, Benurwar M, Borgers M, et al. The mechanism of gamma-secretase dysfunction in familial Alzheimer disease. *EMBO J*. 2012;31(10):2261–74.
- [66] Sudoh S, Kawamura Y, Sato S, Wang R, Saido TC, Oyama F, et al. Presenilin 1 mutations linked to familial Alzheimer's disease increase the intracellular levels of amyloid beta-protein 1-42 and its N-terminally truncated variant(s) which are generated at distinct sites. *J Neurochem*. 1998;71(4):1535–43.
- [67] Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science*. 1995;269(5226):973–7.
- [68] Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, et al. Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nat Med*. 1996;2(8):864–70.
- [69] Steiner H, Capell A, Leimer U, Haass C. Genes and mechanisms involved in beta-amyloid generation and Alzheimer's disease. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(6):266–70.

- [70] Zatti G, Burgo A, Giacomello M, Barbiero L, Ghidoni R, Sinigaglia G, et al. Presenilin mutations linked to familial Alzheimer's disease reduce endoplasmic reticulum and Golgi apparatus calcium levels. *Cell Calcium*. 2006;39(6):539–50.
- [71] Francis YI, Stephanou A, Latchman DS. CREB-binding protein activation by presenilin 1 but not by its M146L mutant. *Neuroreport*. 2006;17(9):917–21.
- [72] Barthet G, Dunys J, Shao Z, Xuan Z, Ren Y, Xu J, et al. Presenilin mediates neuroprotective functions of ephrinB and brain-derived neurotrophic factor and regulates ligand-induced internalization and metabolism of EphB2 and TrkB receptors. *Neurobiol Aging*. 2013;34(2):499–510.
- [73] Armstrong RA. Plaques and tangles and the pathogenesis of Alzheimer's disease. *Folia Neuropathol*. 2006;44(1):1–11.
- [74] Shepherd CE, Gregory GC, Vickers JC, Brooks WS, Kwok JB, Schofield PR, et al. Positional effects of presenilin-1 mutations on tau phosphorylation in cortical plaques. *Neurobiol Dis*. 2004;15(1):115–9.
- [75] Lyall DM, Harris SE, Bastin ME, Munoz Maniega S, Murray C, Lutz MW, et al. Alzheimer's disease susceptibility genes APOE and TOMM40, and brain white matter integrity in the Lothian Birth Cohort 1936. *Neurobiol Aging*. 2014;35(6):1513 e25–33.
- [76] Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health*. 1998;88(9):1337–42.
- [77] Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement*. 2007;3(3):186–91.
- [78] Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*. 2013;80(19):1778–83.
- [79] Mayeux R, Stern Y, Ottman R, Tatemichi TK, Tang MX, Maestre G, et al. The apolipoprotein epsilon 4 allele in patients with Alzheimer's disease. *Ann Neurol*. 1993;34(5):752–4.
- [80] Wang JM, Irwin RW, Brinton RD. Activation of estrogen receptor alpha increases and estrogen receptor beta decreases apolipoprotein E expression in hippocampus in vitro and in vivo. *Proc Natl Acad Sci U S A*. 2006;103(45):16983–8.
- [81] Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat Rev Neurosci*. 2009;10(5):333–44.
- [82] Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. *J Lipid Res*. 2009;50(Suppl):S183–8.

- [83] Castellano JM, Kim J, Stewart FR, Jiang H, DeMattos RB, Patterson BW, et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. *Sci Transl Med*. 2011;3(89):89ra57.
- [84] Sanan DA, Weisgraber KH, Russell SJ, Mahley RW, Huang D, Saunders A, et al. Apolipoprotein E associates with beta amyloid peptide of Alzheimer's disease to form novel monofibrils. Isoform apoE4 associates more efficiently than apoE3. *J Clin Invest*. 1994;94(2):860–9.
- [85] Shen N, Chen B, Jiang Y, Feng R, Liao M, Zhang L, et al. An updated analysis with 85,939 samples confirms the association between CR1 rs6656401 polymorphism and Alzheimer's disease. *Mol Neurobiol*. 2015;51(3):1017–23.
- [86] Liu G, Wang H, Liu J, Li J, Li H, Ma G, et al. The CLU gene rs11136000 variant is significantly associated with Alzheimer's disease in Caucasian and Asian populations. *Neuromolecular Med*. 2014;16(1):52–60.
- [87] Omoumi A, Fok A, Greenwood T, Sadovnick AD, Feldman HH, Hsiung GY. Evaluation of late-onset Alzheimer disease genetic susceptibility risks in a Canadian population. *Neurobiol Aging*. 2014;35(4):936 e5–12.
- [88] Griciuc A, Serrano-Pozo A, Parrado AR, Lesinski AN, Asselin CN, Mullin K, et al. Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. *Neuron*. 2013;78(4):631–43.
- [89] Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, et al. TREM2 variants in Alzheimer's disease. *N Engl J Med*. 2013;368(2):117–27.
- [90] Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med*. 2013;368(2):107–16.
- [91] Ruiz A, Heilmann S, Becker T, Hernandez I, Wagner H, Thelen M, et al. Follow-up of loci from the International Genomics of Alzheimer's Disease Project identifies TRIP4 as a novel susceptibility gene. *Transl Psychiatry*. 2014;4:e358.
- [92] Singaraja RR. TREM2: a new risk factor for Alzheimer's disease. *Clin Genet*. 2013;83(6):525–6.
- [93] Sun M, Zhu M, Chen K, Nie X, Deng Q, Hazlett LD, et al. TREM-2 promotes host resistance against *Pseudomonas aeruginosa* infection by suppressing corneal inflammation via a PI3K/Akt signaling pathway. *Invest Ophthalmol Vis Sci*. 2013;54(5):3451–62.
- [94] Hickman SE, El Khoury J. TREM2 and the neuroimmunology of Alzheimer's disease. *Biochem Pharmacol*. 2014;88(4):495–8.

- [95] Fisher Y, Nemirovsky A, Baron R, Monsonog A. T cells specifically targeted to amyloid plaques enhance plaque clearance in a mouse model of Alzheimer's disease. *PLoS One*. 2010;5(5):e10830.
- [96] Piccio L, Deming Y, Del-Aguila JL, Ghezzi L, Holtzman DM, Fagan AM, et al. Cerebrospinal fluid soluble TREM2 is higher in Alzheimer disease and associated with mutation status. *Acta Neuropathol*. 2016;131(6):925-33.
- [97] Heslegrave A, Heywood W, Paterson R, Magdalinou N, Svensson J, Johansson P, et al. Increased cerebrospinal fluid soluble TREM2 concentration in Alzheimer's disease. *Mol Neurodegener*. 2016;11(1):3.
- [98] Cruchaga C, Kauwe JS, Harari O, Jin SC, Cai Y, Karch CM, et al. GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease. *Neuron*. 2013;78(2):256-68.
- [99] Cirrito JR, Deane R, Fagan AM, Spinner ML, Parsadanian M, Finn MB, et al. P-glycoprotein deficiency at the blood-brain barrier increases amyloid-beta deposition in an Alzheimer disease mouse model. *J Clin Invest*. 2005;115(11):3285-90.
- [100] Jaynes B, Provias J. An investigation into the role of P-glycoprotein in Alzheimer's disease lesion pathogenesis. *Neurosci Lett*. 2011;487(3):389-93.
- [101] Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*. 2013;45(12):1452-8.
- [102] Cacabelos R. Epigenomic networking in drug development: from pathogenic mechanisms to pharmacogenomics. *Drug Dev Res*. 2014;75(6):348-65.
- [103] Cacabelos R, Torrellas C. Epigenetic drug discovery for Alzheimer's disease. *Expert Opin Drug Discov*. 2014;9(9):1059-86.
- [104] Bennett DA, Yu L, Yang J, Srivastava GP, Aubin C, De Jager PL. Epigenomics of Alzheimer's disease. *Transl Res*. 2015;165(1):200-20.
- [105] Wang J, Yu JT, Tan MS, Jiang T, Tan L. Epigenetic mechanisms in Alzheimer's disease: implications for pathogenesis and therapy. *Ageing Res Rev*. 2013;12(4):1024-41.
- [106] Veerappan CS, Sleiman S, Coppola G. Epigenetics of Alzheimer's disease and frontotemporal dementia. *Neurotherapeutics*. 2013;10(4):709-21.
- [107] Mastroeni D, Grover A, Delvaux E, Whiteside C, Coleman PD, Rogers J. Epigenetic mechanisms in Alzheimer's disease. *Neurobiol Aging*. 2011;32(7):1161-80.
- [108] Mill J. Toward an integrated genetic and epigenetic approach to Alzheimer's disease. *Neurobiol Aging*. 2011;32(7):1188-91.
- [109] Graff J, Tsai LH. The potential of HDAC inhibitors as cognitive enhancers. *Annu Rev Pharmacol Toxicol*. 2013;53:311-30.

- [110] Adwan L, Zawia NH. Epigenetics: a novel therapeutic approach for the treatment of Alzheimer's disease. *Pharmacol Ther.* 2013;139(1):41–50.
- [111] Francis YI, Fa M, Ashraf H, Zhang H, Staniszewski A, Latchman DS, et al. Dysregulation of histone acetylation in the APP/PS1 mouse model of Alzheimer's disease. *J Alzheimers Dis.* 2009;18(1):131–9.
- [112] Fang M, Wang J, Zhang X, Geng Y, Hu Z, Rudd JA, et al. The miR-124 regulates the expression of BACE1/beta-secretase correlated with cell death in Alzheimer's disease. *Toxicol Lett.* 2012;209(1):94–105.
- [113] Walker MP, LaFerla FM, Oddo SS, Brewer GJ. Reversible epigenetic histone modifications and Bdnf expression in neurons with aging and from a mouse model of Alzheimer's disease. *Age (Dordr).* 2013;35(3):519–31.
- [114] Ding H, Dolan PJ, Johnson GV. Histone deacetylase 6 interacts with the microtubule-associated protein tau. *J Neurochem.* 2008;106(5):2119–30.
- [115] Ogawa O, Zhu X, Lee HG, Raina A, Obrenovich ME, Bowser R, et al. Ectopic localization of phosphorylated histone H3 in Alzheimer's disease: a mitotic catastrophe? *Acta Neuropathol.* 2003;105(5):524–8.
- [116] Rao JS, Keleshian VL, Klein S, Rapoport SI. Epigenetic modifications in frontal cortex from Alzheimer's disease and bipolar disorder patients. *Transl Psychiatry.* 2012;2:e132.
- [117] Tohgi H, Utsugisawa K, Nagane Y, Yoshimura M, Ukitsu M, Genda Y. The methylation status of cytosines in a tau gene promoter region alters with age to downregulate transcriptional activity in human cerebral cortex. *Neurosci Lett.* 1999;275(2):89–92.
- [118] Wang SC, Oelze B, Schumacher A. Age-specific epigenetic drift in late-onset Alzheimer's disease. *PLoS One.* 2008;3(7):e2698.
- [119] Fusco A, Seminara L, Cavallaro RA, D'Anselmi F, Scarpa S. S-adenosylmethionine/homocysteine cycle alterations modify DNA methylation status with consequent deregulation of PS1 and BACE and beta-amyloid production. *Mol Cell Neurosci.* 2005;28(1):195–204.
- [120] Theuns J, Del-Favero J, Dermaut B, van Duijn CM, Backhovens H, Van den Broeck MV, et al. Genetic variability in the regulatory region of presenilin 1 associated with risk for Alzheimer's disease and variable expression. *Hum Mol Genet.* 2000;9(3):325–31.
- [121] Tanzi RE, Bertram L. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. *Cell.* 2005;120(4):545–55.
- [122] Rauhala HE, Porkka KP, Saramaki OR, Tammela TL, Visakorpi T. Clusterin is epigenetically regulated in prostate cancer. *Int J Cancer.* 2008;123(7):1601–9.
- [123] Zhou XW, Gustafsson JA, Tanila H, Bjorkdahl C, Liu R, Winblad B, et al. Tau hyperphosphorylation correlates with reduced methylation of protein phosphatase 2A. *Neurobiol Dis.* 2008;31(3):386–94.

- [124] Sontag E, Nunbhakdi-Craig V, Sontag JM, Diaz-Arrastia R, Ogris E, Dayal S, et al. Protein phosphatase 2A methyltransferase links homocysteine metabolism with tau and amyloid precursor protein regulation. *J Neurosci*. 2007;27(11):2751–9.
- [125] Sanchez-Mut JV, Aso E, Panayotis N, Lott I, Dierssen M, Rabano A, et al. DNA methylation map of mouse and human brain identifies target genes in Alzheimer's disease. *Brain*. 2013;136(Pt 10):3018–27.
- [126] Van den Hove DL, Kompotis K, Lardenoije R, Kenis G, Mill J, Steinbusch HW, et al. Epigenetically regulated microRNAs in Alzheimer's disease. *Neurobiol Aging*. 2014;35(4):731–45.
- [127] Wu J, Li S, Jia W, Deng H, Chen K, Zhu L, et al. Reduced Let-7a Is Associated with chemoresistance in primary breast cancer. *PLoS One*. 2015;10(7):e0133643.
- [128] Kumar P, Dezso Z, MacKenzie C, Oestreicher J, AgoulNIK S, Byrne M, et al. Circulating miRNA biomarkers for Alzheimer's disease. *PLoS One*. 2013;8(7):e69807.
- [129] Leidinger P, Backes C, Deutscher S, Schmitt K, Mueller SC, Frese K, et al. A blood based 12-miRNA signature of Alzheimer disease patients. *Genome Biol*. 2013;14(7):R78.
- [130] Alexandrov PN, Dua P, Hill JM, Bhattacharjee S, Zhao Y, Lukiw WJ. microRNA (miRNA) speciation in Alzheimer's disease (AD) cerebrospinal fluid (CSF) and extracellular fluid (ECF). *Int J Biochem Mol Biol*. 2012;3(4):365–73.
- [131] Long JM, Lahiri DK. MicroRNA-101 downregulates Alzheimer's amyloid-beta precursor protein levels in human cell cultures and is differentially expressed. *Biochem Biophys Res Commun*. 2011;404(4):889–95.
- [132] Liu W, Liu C, Zhu J, Shu P, Yin B, Gong Y, et al. MicroRNA-16 targets amyloid precursor protein to potentially modulate Alzheimer's-associated pathogenesis in SAMP8 mice. *Neurobiol Aging*. 2012;33(3):522–34.
- [133] Smith P, Al Hashimi A, Girard J, Delay C, Hebert SS. In vivo regulation of amyloid precursor protein neuronal splicing by microRNAs. *J Neurochem*. 2011;116(2):240–7.
- [134] Zong Y, Wang H, Dong W, Quan X, Zhu H, Xu Y, et al. miR-29c regulates BACE1 protein expression. *Brain Res*. 2011;1395:108–15.
- [135] Boissonneault V, Plante I, Rivest S, Provost P. MicroRNA-298 and microRNA-328 regulate expression of mouse beta-amyloid precursor protein-converting enzyme 1. *J Biol Chem*. 2009;284(4):1971–81.
- [136] Zhu HC, Wang LM, Wang M, Song B, Tan S, Teng JF, et al. MicroRNA-195 downregulates Alzheimer's disease amyloid-beta production by targeting BACE1. *Brain Res Bull*. 2012;88(6):596–601.
- [137] Caputo V, Sinibaldi L, Fiorentino A, Parisi C, Catalanotto C, Pasini A, et al. Brain derived neurotrophic factor (BDNF) expression is regulated by microRNAs miR-26a and miR-26b allele-specific binding. *PLoS One*. 2011;6(12):e28656.

- [138] Mohamed JS, Lopez MA, Boriek AM. Mechanical stretch up-regulates microRNA-26a and induces human airway smooth muscle hypertrophy by suppressing glycogen synthase kinase-3beta. *J Biol Chem*. 2010;285(38):29336–47.
- [139] Cogswell JP, Ward J, Taylor IA, Waters M, Shi Y, Cannon B, et al. Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways. *J Alzheimers Dis*. 2008;14(1):27–41.
- [140] Bilen J, Liu N, Burnett BG, Pittman RN, Bonini NM. MicroRNA pathways modulate polyglutamine-induced neurodegeneration. *Mol Cell*. 2006;24(1):157–63.
- [141] Wang WX, Huang Q, Hu Y, Stromberg AJ, Nelson PT. Patterns of microRNA expression in normal and early Alzheimer's disease human temporal cortex: white matter versus gray matter. *Acta Neuropathol*. 2011;121(2):193–205.
- [142] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA*. 1997;278(16):1349–56.
- [143] Payami H, Montee KR, Kaye JA, Bird TD, Yu CE, Wijsman EM, et al. Alzheimer's disease, apolipoprotein E4, and gender. *JAMA*. 1994;271(17):1316–7.
- [144] Damoiseaux JS, Seeley WW, Zhou J, Shirer WR, Coppola G, Karydas A, et al. Gender modulates the APOE epsilon4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. *J Neurosci*. 2012;32(24):8254–62.
- [145] Altmann A, Tian L, Henderson VW, Greicius MD. Alzheimer's disease neuroimaging initiative I. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75(4):563–73.
- [146] Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med*. 1996;334(12):752–8.
- [147] Corder EH, Ghebremedhin E, Taylor MG, Thal DR, Ohm TG, Braak H. The biphasic relationship between regional brain senile plaque and neurofibrillary tangle distributions: modification by age, sex, and APOE polymorphism. *Ann N Y Acad Sci*. 2004;1019:24–8.
- [148] Ryan J, Carriere I, Carcaillon L, Dartigues JF, Auriacombe S, Rouaud O, et al. Estrogen receptor polymorphisms and incident dementia: the prospective 3C study. *Alzheimers Dement*. 2014;10(1):27–35.
- [149] Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA*. 1994;271(13):1004–10.

- [150] Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *J Neurol Neurosurg Psychiatry*. 1999;66(2):177–83.
- [151] Fitzpatrick AL, Kuller LH, Ives DG, Lopez OL, Jagust W, Breitner JC, et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. *J Am Geriatr Soc*. 2004;52(2):195–204.
- [152] Tsvetanov KA, Henson RN, Tyler LK, Razi A, Geerligs L, Ham TE, et al. Extrinsic and intrinsic brain network connectivity maintains cognition across the lifespan despite accelerated decay of regional brain activation. *J Neurosci*. 2016;36(11):3115–26.
- [153] Wilson RS, Scherr PA, Schneider JA, Tang Y, Bennett DA. Relation of cognitive activity to risk of developing Alzheimer disease. *Neurology*. 2007;69(20):1911–20.
- [154] Akbaraly TN, Portet F, Fustini S, Dartigues JF, Artero S, Rouaud O, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. *Neurology*. 2009;73(11):854–61.
- [155] Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol*. 2004;3(6):343–53.
- [156] Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. *JAMA*. 2004;292(12):1447–53.
- [157] Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *JAMA*. 2004;292(12):1454–61.
- [158] Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol*. 2005;161(7):639–51.
- [159] Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med*. 2006;144(2):73–81.
- [160] Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Bianchin M, et al. Physical activity and dementia risk in the elderly: findings from a prospective Italian study. *Neurology*. 2008;70(19 Pt 2):1786–94.
- [161] Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4(8):487–99.
- [162] Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging*. 2000;21(1):49–55.

- [163] Shobab LA, Hsiung GY, Feldman HH. Cholesterol in Alzheimer's disease. *Lancet Neurol.* 2005;4(12):841–52.
- [164] Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol.* 2008;7(2):184–90.
- [165] Gillette Guyonnet S, Abellan Van Kan G, Andrieu S, Barberger Gateau P, Berr C, Bonnefoy M, et al. IANA task force on nutrition and cognitive decline with aging. *J Nutr Health Aging.* 2007;11(2):132–52.
- [166] Heude B, Ducimetiere P, Berr C, Study EVA. Cognitive decline and fatty acid composition of erythrocyte membranes – the EVA study. *Am J Clin Nutr.* 2003;77(4):803–8.
- [167] Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues JF, Renaud S. Fish, meat, and risk of dementia: cohort study. *BMJ.* 2002;325(7370):932–3.
- [168] Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, et al. Dietary patterns and risk of dementia: the Three-City cohort study. *Neurology.* 2007;69(20):1921–30.