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Epigenetic Regulation in Alzheimer's Disease: Roles of DNA Methylation and Histone Regulation

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Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and one of the leading causes of dementia. The most significant known risk factor for AD is aging, and the increasing number of elderly people in low- and middle-income countries leads to an increase in AD incidence. Increasingly, age-related epigenetic changes are recognized as key drivers of the onset and progression of AD. This review examines how epigenetic processes, including DNA methylation and histone modification, affect amyloid-beta (Aβ) generation and clearance and tau protein pathology development, which are the two main features of AD. The genes APP, BACE1, PSEN1, and APOE show abnormal DNA methylation patterns, which result in elevated Aβ production and reduced clearance mechanisms. Alterations in histone acetylation and methylation patterns lead to synaptic dysfunction, which results in memory problems. The study demonstrates that BACE1 and PSEN1 methylation decrease with age and APOE status, which leads to Aβ accumulation. Hippocampal regions show decreased histone acetylation, which blocks vital gene expression required for learning, and tau accumulation results from methylation changes that damage cellular cleaning systems. These findings reveal the significant role of epigenetic processes in AD. A deeper understanding of these mechanisms not only sheds light on disease progression but also opens new pathways for treatment. This review highlights promising epigenetic targets and current challenges, encouraging the continued development of epigenetics-based therapies for AD and related neurodegenerative conditions.

Keywords: Alzheimer's Disease; DNA methylation; Histone modification.

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia and the most prevalent neurodegenerative disorder (NDD) globally. Dementia produces multiple symptoms that affect memory and cause problems with time and space awareness and language and cognitive abilities, and behavioral and personality changes. The World Health Organization (WHO) reported in 2021 that AD causes 60–70% of the 57 million global dementia cases, and age remains the main unchangeable risk factor for dementia [1]. The NIA reports that AD affects 11% of people aged 65 and older, but this number increases to 33% for people aged 85 and above [2]. Most dementia patients, amounting to more than 60% who live in low- and middle-income countries (LMICs), match the worldwide pattern of population aging [1].

The molecular structure of AD shows a sequence of harmful processes that lead to progressive damage of neurons and their operational capabilities. The amyloid cascade hypothesis stands as the main scientific theory that explains how Alzheimer's Disease develops, although researchers have not identified the disease's initial cause. The model shows that β- and γ-secretase failure to properly cleave APP leads to elevated Aβ peptide production and aggregation that forms toxic extracellular plaques, which harm neurons. The model receives support from familial AD (FAD) because the APP and PSEN1, and PSEN2 genes with strongly penetrant mutations lead to increased Aβ formation and aggregation. The main genetic risk factor for infrequent Alzheimer's disease (AD) is the apolipoprotein E ε4 (APOE4) allele because it makes Aβ accumulation worse and reduces its clearance from the brain. The formation of intraneuronal neurofibrillary tangles (NFTs) occurs through tau protein hyperphosphorylation in addition to amyloid disease, which disrupts both axonal transport and synaptic function [3,4]. The brain shows two main types of lesions, which are the lacunar infarcts and the white matter lesions. The lacunar infarcts are small infarcts that occur in the deep parts of the brain and are usually caused by small vessel disease. The white matter lesions are areas of damage to the white matter of the brain and are also caused by small vessel disease. In addition to these signature lesions, chronic neuroinflammation from activated microglia and astrocytes causes ongoing neuronal damage and mitochondrial failure, and oxidative stress leads to synaptic loss and cognitive decline [5]. The complex interplay of these mechanisms results in continuous neurodegeneration of the hippocampus and cortex through microglial and astrocyte activation, which creates the conditions for memory loss and dementia symptoms.

Cellular aging creates an environment that allows neurodegenerative chain reactions to initiate. The brain experiences permanent molecular and cellular alterations during aging, which lead to the formation of AD pathology. Genomic instability increases with age, which results in DNA damage accumulation that affects neurons most severely. The brain damage in AD patients reaches its peak in the hippocampus, which serves as the main memory processing area. DNA methylation drift and histone modification changes that occur during aging will increase the risk of developing Alzheimer's disease [6]. The elevation of HDAC activity results in reduced histone acetylation, which causes decreased synaptic plasticity and more severe memory problems in AD models [7]. The aging process transforms brain structure, which enables the formation of AD characteristic brain damage.

Epigenetics is now recognized as an important factor in the development and progression of AD. The inhibition of HDAC3 results in decreased APP cleavage and increased tau breakdown, and changes in neuroprotective gene expression in laboratory cultures and living organisms. The study shows that HDAC3 controls proteins that contribute to the development of Alzheimer's disease [8]. DNMT inhibitors can reverse the hypermethylation of neuroprotective genes, which enables the reactivation of silenced genes and protects the brain [9]. These findings confirm that epigenetic modulators have potential as therapeutic agents in NDDs like AD. The review accelerates neurodegenerative disease treatment development through epigenetics by studying drugable targets (DNMTs/HDACs/ncRNAs) and assessing preclinical and clinical data, and providing solutions to overcome translational challenges. The review examines epigenetic control in AD by identifying potential drug targets and new research findings, and their application to create treatments.

2. DNA methylation

DNA methylation modifications serve as the first signs of Alzheimer's disease because they affect the formation of amyloid and tau protein abnormalities. DNA methylation functions as a major epigenetic control mechanism that controls gene expression and cellular operations through the process of adding methyl groups to cytosines located in CpG (5'-Cytosine-phosphate-guanosine-3') dinucleotides. The DNA methylation process depends on DNA methyltransferases (DNMTs) enzymes, which contain N-terminal regulatory domains and C-terminal catalytic domains [10]. The DNMT family consists of four mem-

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bers, which include DNMT1 and DNMT3A and DNMT3B, and Dnmt3c. DNMT1 functions to preserve existing methylation patterns, but DNMT3A and DNMT3B perform most of the new methylation processes. The DNA demethylation process includes TET proteins, which convert 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) through their enzymatic activity that oxidizes the methyl group [11]. The conversion process through active DNA demethylation results in modifications to epigenetic markers.

Studies show that Alzheimer's disease (AD) develops because of problems in these systems. Research studies show that AD patients have DNA methylation and hydroxymethylation pattern changes in their brain tissue and blood samples, which indicate widespread disruption of epigenetic control systems [11]. The methylation status of genes, including APP, PSEN, MAPT, and APOE, determines their expression levels, which leads to amyloid-beta accumulation and tau pathology, and neuroinflammatory responses [7]. Research studies have demonstrated that DNA methyltransferases (DNMTs) and Ten-Eleven Translocation (TET) enzymes show irregular activity in AD models, which proves that epigenetic dysregulation plays a role in the disease. DNA methylation patterns show promise as both diagnostic markers and therapeutic targets for Alzheimer's disease treatment, according to these findings [12, 13].

2.1 DNA Methylation Dysregulation in Amyloid-β Homeostasis

Changes in DNA methylation are early signs of Alzheimer's disease. These changes can affect amyloid and tau proteins [14]. More research shows that DNA methylation helps control the amyloid process. When this control is lost, the amount of Aβ increases, and the brain can't clear it properly. This leads to toxic Aβ buildup, which is one of the first changes in Alzheimer's [14]. The buildup of amyloid plaques outside cells is a major sign of the disease. It happens before tau proteins clump inside cells and making this worse. This shows that problems with Aβ control, partly caused by methylation changes, may help trigger the disease [14].

2.1.1 Potentiating Aβ Production

The production of amyloid-beta (Aβ) begins through sequential APP cleavage by enzymes. The amyloidogenic pathway begins with β-secretase (BACE1) cleavage of APP, which produces a soluble fragment and the C99 fragment that remains attached to the membrane. The γ-secretase complex processes C99 to produce Aβ peptides, which primarily consist of Aβ40 and Aβ42, while these peptides show a tendency to form aggregates. The essential role of BACE1 and the γ-secretase complex with PSEN1/PSEN2 units in Aβ production makes them critical targets for epigenetic modifications through DNA methylation to affect amyloid behavior.

Research on DNA methylation has focused on the APP gene as one of its primary subjects. Research shows that Alzheimer's disease patients exhibit lower methylation levels at the APP promoter region in their postmortem brain tissues and blood leukocytes when compared to healthy controls [15,16]. Research findings show conflicting results about methylation patterns because some studies detected increased methylation in temporal cortex regions, but others found no differences in frontal cortex and hippocampal regions [17]. Multiple elements exist that explain the observed discrepancies between studies. The methylation patterns of APP show significant variations between different human tissues according to research [18], while brain region differences make it challenging to perform direct comparisons. Research studies face limitations because they work with small participant groups [19], and postmortem interval (PMI) variations might create sample heterogeneity, although DNA methylation remains stable for at least 72 hours after death [20].

The hypomethylation of the promoter region of BACE1 can enhance its transcriptional activity and upregulate its protein levels. The over-formation of BACE1 will then markedly enhance the APP amyloid protein hydrolysis pathway, leading to the generation of more C99 fragments and consequently greatly augmenting the overall Aβ burden, especially the more aggregation-prone Aβ42. This epigenetic disruption is corroborated by epigenome-wide association studies, which have found significant hypomethylation in enhancer regions of genes like DSCAML1 in the prefrontal cortex of subjects with late-stage AD pathology, causing heightened BACE1 transcription [21]. Interestingly, a study by Su et al. (2024) also found that higher plasma BACE1 activity was associated with neurodegeneration in cerebral small vessel disease, corroborating the wider involvement of BACE1 dysregulation in neuropathological processes outside classical AD [22]. In Alzheimer's mouse models, PSEN1 methylation did not show big changes, so it may not be involved in those models [23]. But in human brain tissue, PSEN1 often has lower methylation in people with Alzheimer's [24]. Also, DNA from the blood of Alzheimer's patients shows lower PSEN1 methylation than in healthy people. This change links to higher PSEN1 gene activity as the disease gets worse [25]. These results show that

PSEN methylation is complex and changes depending on the situation. It may matter more in humans and could work as a sign of disease in blood tests.

2.1.2 Impairing Aβ Clearance

Aβ levels in the brain depend not only on how much is made but also on how much is cleared. DNA methylation also affects genes that help with Aβ clearance.

The APOE ε4 version is the biggest genetic risk factor for late-onset Alzheimer's. This version adds a new CpG methylation site, which makes a different gene control pattern [26, 27]. This region works like an enhancer and changes how the gene is used in different cell types and versions.

In cells like astrocytes and microglia, APOE often has lower methylation. This can change how much APOE is made [28]. The APOE4 protein doesn't clear Aβ well. It may even help Aβ clump together, which causes plaques. APOE methylation also goes down with age. This may raise Alzheimer's risk and affect fat control in the brain [29]. Interestingly, whereas less methylation usually means more APOE can be found in cognitively normal individuals, this correlation is lost in AD brains, indicating that there's disease-specific epigenetic dysregulation [30]. While results between studies sometimes differ due to methodological or sample heterogeneity, cumulative evidence highlights the importance of APOE methylation as a crucial mechanistic link between genetic risk, aging, and Alzheimer's disease pathogenesis. Together, disrupted DNA methylation in genes governing both amyloid production and clearance underscores its central role in AD progression, warranting further exploration of histone modifications.

3. Histone Modification

Histone modifications serve as an important epigenetic regulation method, significantly impacting the development of Alzheimer's disease (AD). These post-translational modifications (PTMs) modify chromatin structure and influence gene accessibility, thereby controlling gene expression programs vital for neuronal activity. Problems with these changes, such as acetylation, methylation, phosphorylation, and ubiquitylation, are now more often linked to memory loss and reduced synaptic plasticity in people with AD.

3.1 Histone Acetylation

Histone acetylation is one of the most studied types of histone changes in Alzheimer's disease [7, 31]. Enzymes like CBP/p300, PCAF, and HDACs help carry out this change. Acetylation removes the positive charge from histones, which loosens the DNA-histone bond, causing chromatin to shift from a condensed state (heterochromatin) to a more relaxed state (euchromatin). In AD, there is a clear imbalance in histone acetylation, though its presentation is complex and varies by specific sites and regions. A major decrease in acetylation, known as hypoacetylation, has been found in memory-related areas like the hippocampus, both in patients and in animal models [7, 31]. For example, mice with the APP/PS1 mutation showed a 50% drop in H4 acetylation in the hippocampus after learning. This drop was linked to weaker brain plasticity and worse memory [7]. Conversely, some studies report that increased acetylation (hyperacetylation) occurs in certain brain regions like the frontal cortex [31]. Although HDAC inhibitors have shown improved cognitive functions in animal models, their non-selective side effects have hindered clinical application, highlighting the need for more targeted therapies and the development of more selective inhibitors.

3.2 Histone Methylation

Histone methylation involves adding methyl groups to lysine or arginine residues on histone tails and is catalyzed by histone methyltransferases (HMTs), which recruit specific proteins that modify chromatin accessibility. Methylation is removed by histone demethylases (HDMs). Depending on the specific amino acid residue and the number of methyl groups (mono-, di-, or trimethylation), these modifications can activate or silence transcription. In AD, several abnormal methylation patterns are identified. Key changes include decreased H3K4me3, typically a marker of active transcription, and increased H3K27me3, usually a marker of transcriptional repression [7]. These changes are thought to contribute to AD development through multiple pathways, including direct alteration of MAPT gene expression and resulting tau protein aggregation, as well as disruption of cellular autophagy, which is essential for clearing Aβ and tau pathologies [7].

3.3 Other Histone Modifications

Other histone modifications can also contribute to AD, although many of the findings are based on limited sample sizes. Histone phosphorylation is frequently linked to DNA damage responses, cell cycle reactivation, and cell death, and increased levels of H3/H4 phosphorylation have been detected in AD brains [7]. Likewise, histone ubiquitylation shows robust increases, particularly at H2A and H2B sites, which may profoundly affect higher-order chromatin structure and gene regulation (Table 1) [7, 31].

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Table 1. Other Histone Modifications in AD

Histone modifications	Tissue type / Model	Main findings	References
H2B ubiquitination (K120)	Human postmortem frontal cortex	91% increase in AD cases compared to controls	[32]
H2A ubiquitination (K119)	Human postmortem cortex	~50% increase in ubiquitination; ~2-fold increase in mono/penta-ubiquitinated H2A	[33]
H2AX phosphorylation (S139)	Cortical/hippocampal astrocytes from AD patients	Increased levels compared to control individuals; indicate DNA damage response and astrocyte involvement	[34]
H3 phosphorylation (S10)	Cytoplasm of hippocampal neurons in AD patients	Increased levels; suggests aberrant cell cycle re-entry and neuronal death	[35]
H3 phosphorylation (S28)	Implicated in learning and memory pathways; regulates cFOS expression	Linked to memory formation, potential dysregulation in AD	[36]
H4 phosphorylation (S47)	Human AD brain samples	Phosphorylation levels positively correlate with AD progression	[37]

4. Conclusion

This review highlights the importance of epigenetic regulation in the development of Alzheimer's disease. Changes in gene regulation, especially DNA methylation in genes like APP, BACE1, PSEN1, and APOE, affect how much Aβ is made and how well it is removed. These changes can start the disease early. Meanwhile, histone modifications, especially lowered acetylation and ectopic methylation, disturb the gene activity needed for keeping brain connections healthy and protecting brain cells. This can lead to memory loss and cognitive disorders.

By integrating the latest evidence, we demonstrate that certain epigenetic changes can serve as both biomarkers and treatment targets. Differential BACE1 and PSEN1 methylation promotes Aβ production, while APOE methylation affects the lipid metabolism and clearance capacity. Additionally, reduced histone acetylation in brain regions causes impaired synaptic plasticity. These changes further influence tau protein regulation and autophagy through alterations in methylation.

The main significance of the study in epigenetic regulations is the potential for clinical application. Targeting epigenetic modulators, particularly DNMTs and HDACs, may help reverse disease-driving alterations and rescue neuronal function. Prospective treatment development needs much greater specificity and lesser systemic toxicity. Ongoing studies focused on deciphering the functioning of the epigenetic machinery possess the promise for new precision therapies for Alzheimer's disease, as well as its prevention and diagnosis.

References

[1] Dementia. Retrieved August 17, 2025, from https://www.who.int/news-room/fact-sheets/detail/dementia

[2] National Institute on Aging. Alzheimer's disease fact sheet. 2023, April 5. https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet

[3] Knopman David S., Amieva Helene, Petersen Ronald C., Chételat Gael, Holtzman David M., Hyman Bradley T., Nixon Roger A., Jones David T. Alzheimer disease. Nature Reviews Disease Primers, 2021, 7(1), 33. https://doi.org/10.1038/s41572-021-00269-y

[4] Scheltens Philip, De Strooper Bart, Kivipelto Miia, Holstege Harry, Chételat Gael, Teunissen Charlotte E., Cummings Jeffrey, van der Flier W. M. Alzheimer's disease. Lancet, 2021, 397(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4

[5] Mary Alice, Mancuso Raffaele, Heneka Michael T. Immune Activation in Alzheimer Disease. Annual Review of Immunology, 2024, 42(1), 585–613. https://doi.org/10.1146/annurev-immunol-101921-035222

[6] Mattson Mark P., Arumugam Thiruma V. Hallmarks of Brain Aging: Adaptive and Pathological Modification by Metabolic States. Cell Metabolism, 2018, 27(6), 1176–1199. https://doi.org/10.1016/j.cmet.2018.05.011

[7] De Plano Lucia M., Saitta Angela, Oddo Salvatore, Caccamo Angelo. Epigenetic Changes in Alzheimer's Disease: DNA Methylation and Histone Modification. Cells, 2024, 13(8), 719. https://doi.org/10.3390/cells13080719

[8] Janczura K. J., Volmar C.-H., Sartor G. C., Rao S. J., Ricciardi N. R., Lambert G., Brothers S. P., Wahlestedt C. RETRACTED: Inhibition of HDAC3 reverses Alzheimer's

disease-related pathologies in vitro and in the 3xTg-AD mouse model. Proceedings of the National Academy of Sciences, 2018, 115(47). https://doi.org/10.1073/pnas.1805436115

[9] Lyko Friedrich. The DNA methyltransferase family: a versatile toolkit for epigenetic regulation. Nature Reviews Genetics, 2018, 19(2), 81–92. https://doi.org/10.1038/nrg.2017.80

[10] Gujar Hemant, Weisenberger Daniel J., Liang Gang. The Roles of Human DNA Methyltransferases and Their Isoforms in Shaping the Epigenome. Genes, 2019, 10(2), 172. https://doi.org/10.3390/genes10020172

[11] Martínez-Iglesias Oscar, Carrera Irene, Carril Juan C., Fernández-Novoa Lidia, Cacabelos Nicolau, Cacabelos Ramón. DNA Methylation in Neurodegenerative and Cerebrovascular Disorders. International Journal of Molecular Sciences, 2020, 21(6), 2220. https://doi.org/10.3390/ijms21062220

[12] Zhang Hao, Zhang Xiaoxing, Clark E., Mulcahey M., Huang S., Shi Y. G. TET1 is a DNA-binding protein that modulates DNA methylation and gene transcription via hydroxylation of 5-methylcytosine. Cell Research, 2010, 20(12), 1390–1393. https://doi.org/10.1038/cr.2010.156

[13] Cochran Jason N., Geier Emily G., Bonham Laura W., Newberry James S., Amaral Michael D., Thompson Michelle L., Lasseigne Brandon N., Karydas Aristeidis M., Roberson Erik D., Cooper Grant M., Rabinovici Gil D., Miller Bruce L., Myers Richard M., Yokoyama J. S., Alzheimer's Disease Neuroimaging Initiative. Non-coding and Loss-of-Function Coding Variants in TET2 are Associated with Multiple Neurodegenerative Diseases. American Journal of Human Genetics, 2020, 106(5), 632–645. https://doi.org/10.1016/j.ajhg.2020.03.010

[14] Jucker Mathias, Walker Lawrence C. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature, 2013, 501(7465), 45–51. https://doi.org/10.1038/nature12481

[15] West Robert L., Lee John M., Maroun L. E. Hypomethylation of the amyloid precursor protein gene in the brain of an Alzheimer's disease patient. Journal of Molecular Neuroscience, 1995, 6(2), 141–146. https://doi.org/10.1007/BF02736773

[16] Hou Yafei, Chen Hong, He Qiang, Jiang Wei, Luo Tao, Duan Jin, Mu Nian, He Yi, Wang Hong. Changes in methylation patterns of multiple genes from peripheral blood leucocytes of Alzheimer's disease patients. Acta Neuropsychiatrica, 2013, 25(2), 66–76. https://doi.org/10.1111/j.1601-5215.2012.00662.x

[17] Barrachina Maria, Ferrer Isidre. DNA methylation of Alzheimer disease and tauopathy-related genes in postmortem brain. Journal of Neuropathology and Experimental Neurology, 2009, 68(8), 880–891. https://doi.org/10.1097/NEN.0b013e3181af2e46

[18] Rogaev Eugene I., Lukiw Walter J., Lavrushina Olga, Rogaeva Ekaterina A., St George-Hyslop Peter H. The upstream promoter of the beta-amyloid precursor protein gene (APP) shows differential patterns of methylation in human brain. Genomics, 1994, 22(2), 340–347. https://doi.org/10.1006/geno.1994.1393

[19] Li Qian, Hermanson Patrick J., Springer Nathan M. Detection of DNA Methylation by Whole-Genome Bisulfite Sequencing. Methods in Molecular Biology, 2018, 1676, 185–196. https://doi.org/10.1007/978-1-4939-7315-6_11

[20] Jarmasz Jason S., Stirton H., Davie J. R., Del Bigio M. R. DNA methylation and histone post-translational modification stability in post-mortem brain tissue. Clinical Epigenetics, 2019, 11(1), 5. https://doi.org/10.1186/s13148-018-0596-7

[21] Hampel Henrik, Vassar Robert, De Strooper Bart, Hardy John, Willem Marc, Singh Neeraj, Zhou Jin, Yan Rong, Vanmechelen Eric, De Vos An, Nisticò Rita, Corbo Michele, Imbimbo Biagio P., Streffer Jens, Voytyuk I., Timmers Maartje, Tahami Monfared A. A., Irizarry Manuel, Albala B., Koyama A., … Vergallo Alessandro. The β-Secretase BACE1 in Alzheimer's Disease. Biological Psychiatry, 2021, 89(8), 745–756. https://doi.org/10.1016/j.biopsych.2020.02.001

[22] Su Yan, Wang Qi, Gao Feng, Xu Jian, Fu Jie, Ying Yu, Xia Yan, Wang Xi, Dong Qun, Shen Yi, Cheng Xia. Increased Plasma β-Secretase 1 Activity Correlates With Neurodegeneration in Cerebral Small Vessel Disease. Journal of the American Heart Association, 2024, 13(24), e036204. https://doi.org/10.1161/JAHA.124.036204

[23] Fuso Alessio, Cavallaro Rosa A., Nicolia Valentina, Scarpa Salvatore. PSEN1 promoter demethylation in hyperhomocysteinemic TgCRND8 mice is the culprit, not the consequence. Current Alzheimer Research, 2012, 9(5), 527–535. https://doi.org/10.2174/156720512800618053

[24] Bakulski Kelly M., Dolinoy Dana C., Sartor Mary A., Paulson H. L., Konen J. R., Lieberman A. P., Albin R. L., Hu H., Rozek L. S. Genome-wide DNA methylation differences between late-onset Alzheimer's disease and cognitively normal controls in human frontal cortex. Journal of Alzheimer's Disease, 2012, 29(3), 571–588. https://doi.org/10.3233/JAD-2012-111223

[25] Monti Nicola, Cavallaro Rosa A., Stoccoro Anna, Nicolia Valentina, Scarpa Salvatore, Kovacs Gabor G., Fiorenza Maria T., Lucarelli Marco, Aronica Eleonora, Ferrer Isidre, Coppedè Fabio, Troen Arlin M., Fuso Alessio. CpG and non-CpG Presenilin1 methylation pattern in course of neurodevelopment and neurodegeneration is associated with gene expression in human and murine brain. Epigenetics, 2020, 15(8), 781–799. https://doi.org/10.1080/15592294.2020.1722917

[26] Sims Rebecca, Hill Michael, Williams Joanne. The multiplex model of the genetics of Alzheimer's disease. Nature Neuroscience, 2020, 23(3), 311–322. https://doi.org/10.1038/s41593-020-0599-5

ISSN 2959-409X

[27] Yu Chia-Wei E., Cudaback E., Foraker J., Thomson Z., Leong L., Lutz F., Gill J. A., Saxton A., Kraemer B., Navas P., Keene C. D., Montine T., Bekris L. M. Epigenetic signature and enhancer activity of the human APOE gene. Human Molecular Genetics, 2013, 22(24), 5036–5047. https://doi.org/10.1093/hmg/ddt354

[28] Tulloch J., Leong L., Thomson Z., Chen S., Lee E. G., Keene C. D., Millard S. P., Yu C. E. Glia-specific APOE epigenetic changes in the Alzheimer's disease brain. Brain Research, 2018, 1698, 179–186. https://doi.org/10.1016/j.brainres.2018.08.006

[29] Ma Yan, Smith C. E., Lai Chao-Qiang, Irvin M. R., Parnell L. D., Lee Y. C., Pham L., Aslibekyan S., Claas S. A., Tsai M. Y., Borecki I. B., Kabagambe E. K., Berciano S., Ordovás J. M., Absher D. M., Arnett D. K. Genetic variants modify the effect of age on APOE methylation in the Genetics of Lipid Lowering Drugs and Diet Network study. Aging Cell, 2015, 14(1), 49–59. https://doi.org/10.1111/acel.12293

[30] Lee E. G., Tulloch J., Chen S., Leong L., Saxton A. D., Kraemer B., Darvas M., Keene C. D., Shutes-David A., Todd K., Millard S., Yu C. E. Redefining transcriptional regulation of the APOE gene and its association with Alzheimer's disease. PLoS One, 2020, 15(1), e0227667. https://doi.org/10.1371/journal.pone.0227667

[31] Xiao Xiaojing, Liu Xiang, Jiao Baohong. Epigenetics: Recent Advances and Its Role in the Treatment of Alzheimer's Disease. Frontiers in Neurology, 2020, 11, 538301. https://doi.org/10.3389/fneur.2020.538301

[32] Anderson K. W., Turko I. V. Histone post-translational modifications in frontal cortex from human donors with Alzheimer's disease. Clinical Proteomics, 2015, 12, 26. https://doi.org/10.1186/s12014-015-9098-1

[33] Guo Y., Chomiak A. A., Hong Y., Lowe C. C., Kopsidas C. A., Chan W. C., Andrade J., Pan H., Zhou X., Monuki E. S., Feng Y. Histone H2A ubiquitination resulting from Brap loss of function connects multiple aging hallmarks and accelerates neurodegeneration. iScience, 2022, 25(7), 104519. https://doi.org/10.1016/j.isci.2022.104519

[34] Myung N. H., Zhu X., Kruman I. I., Castellani R. J., Petersen R. B., Siedlak S. L., Perry G., Smith M. A., Lee H. G. Evidence of DNA damage in Alzheimer disease: phosphorylation of histone H2AX in astrocytes. Age, 2008, 30(4), 209–215. https://doi.org/10.1007/s11357-008-9050-7

[35] Ogawa Osamu, Zhu X., Lee H. G., Raina A., Obrenovich M. E., Bowser R., Ghanbari H. A., Castellani R. J., Perry G., Smith M. A. Ectopic localization of phosphorylated histone H3 in Alzheimer's disease: a mitotic catastrophe?. Acta Neuropathologica, 2003, 105(5), 524–528. https://doi.org/10.1007/s00401-003-0684-3

[36] Lau P. N., Cheung P. Histone code pathway involving H3 S28 phosphorylation and K27 acetylation activates transcription and antagonizes polycomb silencing. Proceedings of the National Academy of Sciences of the United States of America, 2011, 108(7), 2801–2806. https://doi.org/10.1073/pnas.1012798108

[37] Chaput D., Kirouac L., Stevens S. M., Jr, Padmanabhan J. Potential role of PCTAIRE-2, PCTAIRE-3 and P-Histone H4 in amyloid precursor protein-dependent Alzheimer pathology. Oncotarget, 2016, 7(8), 8481–8497. https://doi.org/10.18632/oncotarget.7380