

Molecular Epigenetics in Learning Processes: A Systematic Literature Review

Misbahul Jannah¹, Yokhebed², M. Noris^{3*}, Margiyono Suyitno⁴,

¹Department of Science Education, Universitas Islam Negri Ar-Raniry, Banda Aceh, Indonesia

²Department of Science Education, Faculty of Teacher and Training Education, Universitas Tanjungpura, Pontianak, West Kalimantan, Indonesia

^{3*}Department of Master of Pedagogy, Faculty of Postgraduate Studies, Universitas Muhammadiyah Bima, Kota Bima, West Nusa Tenggara, Indonesia

⁴Department of Elementary Madrasah Teacher Education, Faculty of Tarbiyah, STIT Madina, Sragen, Jawa Tengah, Indonesia

Email All of Authors :

misbahulj@ar-raniry.ac.id^{1*}, yokhebed@fkip.untan.ac.id², mnoris@umbima.ac.id³, suyitno1974@gmail.com⁴

Receive: January, 2026 Accepted: June, 2026

Revision : June, 2026 Available Online : June, 2026

Abstract

Many DNA-binding transcription factors that control gene expression during learning have been identified to date. These changes, which change the DNA-histone interactions in nucleosomes, include acetylation, methylation, phosphorylation, and ubiquitylation that are mediated by enzymes. The purpose of this work is to identify molecular epigenetics in learning. Systematic literature review (SLR) was employed in the study methodology with assistance of the vosviewer program. previous ten years, the english language, and open access were established as inclusion and exclusion criteria. The analysis's findings demonstrated that the distribution of studies on molecular epigenetics in learning varied, with a high of 2022 (208 articles) and low 2017 (68 articles) studies with 9 clusters. Two clusters, cluster 7 (18 items) and cluster 8 (17 items), are devoted to learning. In order to help instructors concentrate on the process of students' memory performance, the research implications serve as a reference when thinking about epigenetic aspects in learning.

Keywords: DNA Methylation, Epigenetic Memory, Epigenetics in Learning, Epigenetics Procces, Long Therm-Memory

I. INTRODUCTION

Epigenetic processes, which control gene expression and chromatin remodeling, are essential for the development of learning and memory. Important mechanisms in memory control include DNA methylation, histone methylation, and histone acetylation (Bayraktar & Kreutz, 2018; Kupke et al.,

2024; Tiffon, 2018). According to (Bayraktar & Kreutz, 2018; Pečarič, 2023), these epigenetic changes might react dynamically to neural stimulation, changing the gene expression patterns that enable the consolidation and preservation of long-term memory. According to (Bartra et al., 2022; Wibowo et al., 2016; W. Xu et al., 2016), the epigenetic machinery has two basic functions: it acts as a "gating" mechanism to control activity-

triggered gene expression and as a "stabilizing" component to preserve cellular and molecular alterations brought on by memory-related events. Knowing these epigenetic mechanisms offers insights into how long-term memories are formed and stored, as well as possible targets for treatment in neurological conditions exhibiting memory-related symptoms (Deng et al., 2023; Grigorenko et al., 2016; Kim & Kaang, 2017). According to (Creighton et al., 2020; Zovkic et al., 2013), more studies in neuroepigenetics may clarify the precise genetic and temporal processes driving memory creation and preservation.

Long-term memory development and maintenance depend heavily on epigenetic regulation, particularly chromatin state, which controls gene expression and preserves cellular alterations. Changes in chromatin state and gene expression patterns brought about by neural activity are critical for the establishment of memory (Gulmez Karaca et al., 2018; Pal et al., 2023). Mechanistic insights into the establishment of long-term memory may be obtained by identifying the epigenetic regulators and signaling pathways involved in memory-related epigenetic controls (Fan et al., 2022; Lee et al., 2019).

Learning and memory processes are regulated by epigenetic modifications such as DNA methylation, histone methylation, and histone acetylation (Dion et al., 2022; O'Geen et al., 2019; Srivas & Thakur, 2017; Todorov & Cunha, 2019; X. Xu, 2015). A crucial epigenetic process for memory and learning is chromatin remodeling, which entails 3D structural alterations in chromatin. The diseases associated with neurological illnesses can also be attributed to epigenetic systems that govern memory and learning. Considering how crucial epigenetics is to be learning. Thus, this study's goal is to examine how epigenetics affects learning

II. LITERATURE STUDY

This section reviews relevant theories, concepts, and previous studies related to the research topic. The literature study aims to identify research gaps, establish the theoretical foundation, and position the current study within existing scholarly work. Relevant and recent sources are critically analyzed to support the research framework and justify the significance of the study.

III. METHOD

A. Research Design

This study is a type of descriptive qualitative research through a systematic review of literature review using the protocol developed by (Noris, 2024) to achieve the proposed objectives. In this study, researchers conducted a comprehensive search of articles in the

Scopus database by entering the keywords "epigenetic" AND "in" AND "learning". The search results were then collected in CSV form which were then visualized and analyzed with Vosviewers software.

B. Research Criteria

The research documents that were searched by researchers included documents published during the period 2015-2024 (until August), documents in the form of final articles, in English, and containing the keywords "epigenetic" AND "in" AND "learning". The search results obtained 1008 documents. The researcher then determined the inclusion and exclusion criteria to limit the search in the database to obtain accurate results. Inclusion criteria include research containing the keywords "Molecular" and "Epigenetics" and "in" and "Learning" in the title, abstract, and keywords, research from 2015-2024, English-language research, and articles that can be accessed openly. Anything other than that was an exclusion criteria. The research procedure followed the PRISMA (Noris, 2024). See Fig. 1.

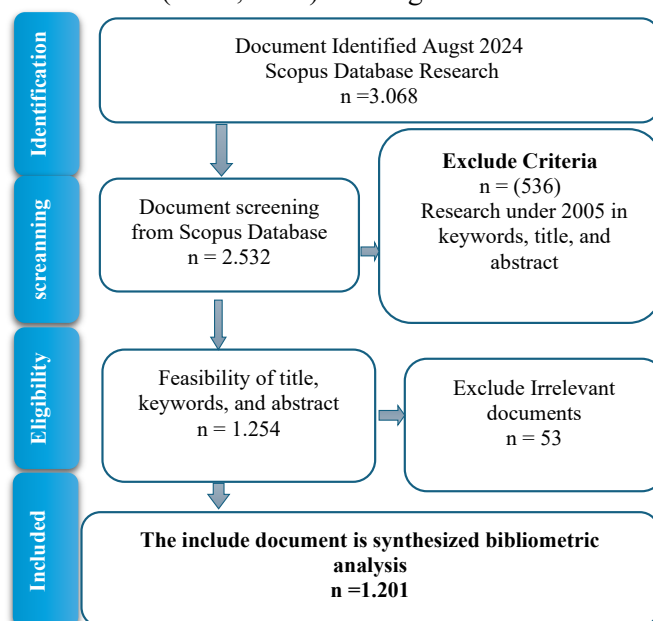


Figure 1. The research procedure followed the PRISMA (Noris, 2024)

C. Research Questions

- RQ1** : Research distribution from the last ten years (2015-2024)?
- RQ2** : Distribution of keywords in epigenetics in learning research?
- RQ3** : Subject areas of molecular epigenetics in learning research from the last ten years (2015-2024)?
- RQ4** : Countries and Autors with the most contributions to molecular epigenetics in learning research?

IV. RESULT AND DISCUSSION

A. Distribution of Molecular Epigenetics Research in the last 10 Years

The distribution of research on molecular epigenetics in learning is fluctuating, indicated by the distribution of research peaking in 2022 with 208 studies, then in 2023 it decreased with 194 studies. See fig 2.

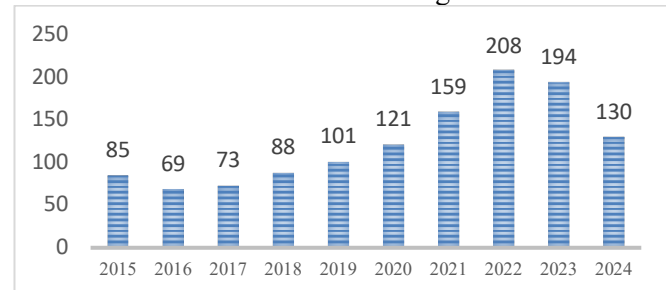


Figure 2. Distribution of Research in the last ten years (as of August 2024)

The distribution of research on molecular epigenetics in learning is fluctuating, indicated by the distribution of research peaking in 2022 with 208 studies, then in 2023 it decreased with 194 studies. Meanwhile, in 2024, which was detected as of August around 130 studies and did not rule out the possibility of experiencing a significant increase. The results of the analysis using vosviewer can be seen in Figure 3.

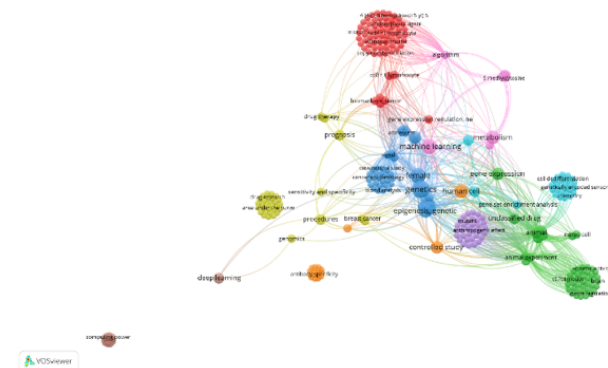


Figure 3. Distribution of research on molecular epigenetics in learning

The results of the analysis using vosviewer show that the study consists of 9 clusters. Cluster 1 consists of 65 items (red color), cluster 2 consists of 49 items (green color), cluster 3 consists of 42 items (dark blue color), cluster 4 consists of 37 items (yellow color), cluster 5 consists of 33 items (purple color), cluster 6 consists of 29 items (light blue color), cluster 7 consists of 18 items (orange color), cluster 8 consists of 17 items (brown color), and cluster 9 consists of 13 items (pink color).

B. Distribution of Keywords in Epigenetics in Learning Research

For measurements, use S.I Units (System

International units). Measurement should be abbreviated (e.g., mm, kcal, etc.) in accordance with the Style Manual for Biological Sciences and using the metric system. Do not begin sentences with a numerical figure. When heading a sentence, numbers should be spelled out.

The analysis results show that keywords that focus on learning appear 81 times with keywords Learning, Memory, Cognitive, Deep Learning, Machine Learning, while those that focus on molecular epigenetics appear 529 times with different keywords such as genetic, DNA Methylation, Genetic Epigenesis, Protein Expression. See fig 4.

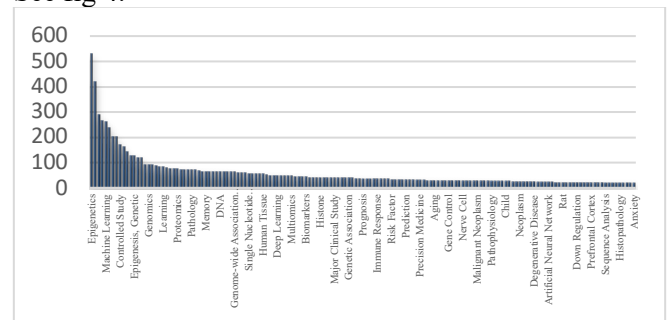


Figure 4. Keywords identified in all molecular epigenetics in learning articles

Memory development and synaptic plasticity are regulated by DNA methylation processes (Grinkevich, 2014; Van Assche et al., 2023). Across paradigms and brain areas, epigenetic mechanisms such as DNA methylation and histone modifications are ubiquitous in learning and memory. Transient alterations in the hippocampus assist early memory consolidation, whereas permanent changes in the cortex support long-term memory preservation. Epigenetic modifications are dynamically controlled in a temporally and geographically specific way. Upstream signaling cascades control epigenetic alterations by defining specific "histone codes" associated with different forms of memory (Singh et al., 2023).

Long-term memory development and maintenance depend heavily on epigenetic regulation, particularly chromatin state, which controls gene expression and preserves cellular alterations. Changes in chromatin state and gene expression patterns brought about by neural activity are critical for the establishment of memory. Mechanistic insights into the establishment of long-term memory may be obtained by identifying the epigenetic regulators and signaling pathways involved in memory-related epigenetic controls (Chen et al., 2018; Sanders et al., 2019).

Mature neural learning genes, such as BDNF, are specifically designed to have "bivalent domains" - rapid transcriptional activation or repression in response to external cues. Dynamic DNA methylation/demethylation and histone modifications control the BDNF gene,

allowing for rapid shifts in gene expression during memory and learning. The regulation of the chromatin landscape and accessibility of learning genes, such as BDNF, during the learning process is largely dependent on enzymes such as Tet1 and signaling pathways such as ERK1/2 (Blough & Wu, 2011; Tchantchou et al., 2023). During the creation of memories, the hippocampus exhibits an increase in histone H3 lysine K4 (H3K4) methylation. Human cognitive disorders are associated with mutations in H3K4 methylation modifiers, such as methyltransferases and demethylases, which are necessary for memory formation. The majority of H3K4 demethylases and all known H3K4 methyltransferases have been linked to cognitive impairment in neurological or mental diseases (El-Sayed et al., 2013; Hörmanseder et al., 2017; Mitchell et al., 2018; Smukowski Heil, 2014).

An essential modulator of memory, learning, and neural plasticity is the m6A epitranscriptome. Human cognitive problems have been connected to disruptions in the m6A epitranscriptome (Li et al., 2021; Mahinfar et al., 2021; Widagdo et al., 2022; C. Xu et al., 2022). Neural plasticity and memory formation are influenced by changes in RNA function, specifically in relation to translation, localization, and structure. Without communicating back to the nucleus, RNA alterations offer a quick, context-dependent method of controlling gene expression in neurons. Determining the molecular processes behind learning and memory will need an understanding of the brain's epitranscriptomic environment (Mirzaeicheshmeh et al., 2021; Wang et al., 2021).

C. Subject areas of molecular epigenetics in learning research from the last ten years

Epigenetic regulation plays a critical role in maintaining long-term changes in gene expression that underlie the formation and stabilization of long-term memory. Research related to molecular epigenetics in learning is dominated by the research area of medicine (25%), while its contribution in education can be seen in chemistry (4.0%) and Other (8.6%) talking about learning. See figure 5.

Conducted a noteworthy examination of the diverse epigenetics literature, delineating four main subfields of epigenetics research: gene expression, molecular epigenetics, clinical epigenetics, and epigenetic epidemiology (Löwy, 2011). Researchers have concentrated especially on cancer (Sajani et al., 2020), and there is a great deal of hope for potential treatments in this field (Pickersgill, 2020). For example, the multinational pharmaceutical company (Allain et al., 2007) is presently concentrating its cancer pipeline on three areas, one of which being epigenetics. Scientists studying other disorders are also growing more

interested in the potential of exploiting epigenetic systems as therapy targets, partly because of the investments and advancements made in epigenetics-related cancer research.

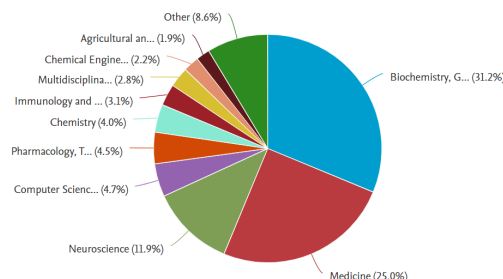


Figure 5. Subject areas of molecular epigenetics in learning research from 2015-2024 (as of August 2024)

As a result of the presumed psychosocial changes that such parental instruction will entail, educational methods have occasionally come to be portrayed as a way of bringing about good changes to children's bodies that will boost their "life chances." As noted by social psychologist and bioethicist "any program of maternal support and education based around epigenetic theories deserves some scrutiny," even though these treatments are being portrayed as socially and politically progressive. This is especially critical in light of the extremely concerning past of biological science enrollment in social policy programs (Rose and Rose, 2014; see also Gillies et al., 2018).

In the context of educational discourse, several researchers have started to include epigenetic concepts and findings to bolster broader assertions on the necessity of addressing the structural inequities that are ingrained in a great deal of educational practice. According to sociologists (Korous et al., 2023), for example, "it appears that social factors, including education, not only may nurture native ability, but they may cause the very native ability they later nurture." Their argument is based on epigenetic research (Kerr et al., 2019; Pickersgill, 2020).

D. Subject areas of molecular epigenetics in learning research from 2015-2024

The country with the most contributions in epigenetic research in learning is the United States with around 252 documents, then China with 68 documents, United Kingdom and Germany with 60 documents. Spain, Italy, France, Canada, Switzerland, and Australia with less than 50 documents. See figure 6.

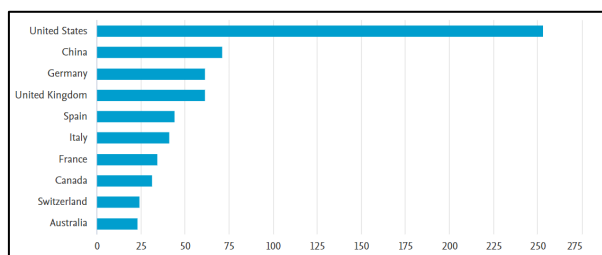


Figure 6. Countries and Author with the most contributions to molecular epigenetics in learning research?

The hippocampal area is one of the brain regions involved in memory allocation. Pyramidal cells in the hippocampus CA1 region undergo structural alterations at the dendritic level and generate new synaptic connections when neurons in this area are recruited to store memory traces. Pre-synaptic glutamate release at gap junctions, post-synaptic activation of N-methyl-D-aspartate and AMPA receptors and downstream signaling cascades are all components of synaptic transmission.

Protein kinase A (PKA) and mitogen-activated protein kinase (MAPK) are triggered by CaMKII, which is activated by Ca²⁺ entering the cytoplasm through N-methyl-D-aspartate receptors. Activated MAPKs then promote CREB-mediated transcription in the nucleus, since CREB is a transcription factor that can lead to the creation of proteins, such as BDNF, c-fos, and tyrosine hydroxylase. Increased synaptic strength at dendritic locations is also dependent on local translation, which occurs independently of somatic transcription (Grinkevich, 2014). All things considered, AMPA receptor insertion and neurotransmitter responses are facilitated by newly generated proteins through their involvement in processes including receptor trafficking and cytoskeletal scaffolding. These anatomical modifications enable the preservation of L-LTP, which is thought to be the cellular foundation of memory (Guadagno et al., 2020; Hiester et al., 2018).

Table 1. Review of molecular epigenetic research in learning.

Title	Abstract summary	Main findings	References
The role of epigenetic regulation in learning and memory	Epigenetic regulation plays a critical role in retaining long-term changes in gene expression that underlie the formation and stabilization of long-term memory.	- Epigenetic regulation, specifically chromatin state, plays a critical role in both the formation and stabilization of long-term memories through regulating gene expression and maintaining cellular changes. - Neuronal activation leads to changes in chromatin status and gene expression profiles, which are important for memory formation. - Identifying the epigenetic regulators and signaling pathways involved in memory-related epigenetic regulations could provide mechanistic insights into the formation of long-term memory.	(Guan et al., 2015)
Epigenetic regulation of cognition: A circumscribed review of the field	Epigenetic mechanisms in the brain, including DNA methylation, histone modification, and non-coding RNA, regulate learning, memory, and other cognitive functions.	- Epigenetic processes in the brain play a role in learning, memory consolidation, and the transmission of acquired memories across generations. - Neuronal activation regulates the dynamics of the epigenome, which in turn alters gene expression profiles, suggesting a key role of epigenetic mechanisms in cognitive processes. - Epigenetic regulation impacts neuronal action, and this bidirectional relationship between epigenetics and neuronal function underlies learning, memory, and other cognitive processes.	(Grigorenko et al., 2016)
Epigenetic regulation and chromatin remodeling in learning and memory	Epigenetic processes like DNA methylation, histone methylation, and histone acetylation regulate gene expression to influence learning and memory formation.	- Epigenetic changes, including DNA methylation, histone methylation, and histone acetylation, are important for regulating learning and memory processes. - Chromatin remodeling, which involves 3D structural changes in chromatin, is a key epigenetic process that is important for learning and memory. - Epigenetic mechanisms that control learning and memory can also contribute to the pathologies of neurological disorders.	(Grigorenko et al., 2016)
Epigenetic regulation of memory formation and maintenance.	Epigenetic mechanisms like DNA methylation and histone modifications regulate gene transcription and are important for	- Epigenetic mechanisms, including DNA methylation and histone modifications, play a ubiquitous role in learning and memory across different paradigms and brain regions. - Epigenetic modifications are dynamically regulated in a temporally and spatially specific manner, with transient	(Zovkic et al., 2013)

	memory formation and maintenance.	changes in the hippocampus supporting initial memory consolidation and persistent changes in the cortex supporting long-term memory maintenance. Epigenetic modifications are regulated by upstream signaling cascades, which establish precise "histone codes" that correspond to particular types of memory.	
Primetime for Learning Genes	Epigenetic mechanisms like bivalent chromatin domains allow learning genes in mature neurons to rapidly respond to environmental stimuli.	- Learning genes in mature neurons, such as BDNF, are uniquely suited to contain "bivalent domains" that allow rapid transcriptional activation or repression in response to environmental stimuli. - The BDNF gene is regulated by dynamic DNA methylation/demethylation and histone modifications that enable rapid changes in gene expression during learning and memory. - Enzymes like Tet1 and signaling pathways like ERK1/2 play a key role in regulating the chromatin landscape and accessibility of learning genes like BDNF during the learning process.	(Keifer , 2017)
Epigenetic Mechanisms of Learning and Memory: Implications for Aging	Epigenetic mechanisms are important for memory formation, and their age-related changes contribute to cognitive decline.	- Epigenetic mechanisms, including DNA methylation, histone modifications, and histone variants, play a key role in regulating memory formation and maintenance. - Aging is associated with dysregulation of the epigenome, which may contribute to age-related memory decline. - Argeting epigenetic mechanisms, such as histone acetylation and histone variants, may have therapeutic potential for treating age-related cognitive impairment.	(Creighton et al., 2020)
Drugging the methylome: DNA methylation and memory	DNA methylation mechanisms are important regulators of synaptic plasticity and memory formation.	- DNA methylation mechanisms are important regulators of non-Hebbian plasticity and a fundamental link between synaptic plasticity and metaplasticity. - Altering DNA methylation within memory circuits is necessary for memory formation. - The dynamic regulation of DNA methylation states is required for synaptic scaling, a form of non-Hebbian plasticity.	(Sweatt., 2016)
How the epigenome integrates information and reshapes the synapse	Epigenetic mechanisms, including histone modification and DNA methylation, dynamically regulate gene expression required for memory formation.	- Epigenetic mechanisms like histone modification, DNA methylation, and nucleosome remodeling dynamically regulate gene expression required for memory formation. - The study examines how learning experiences are integrated at the level of both chromatin structure and synaptic function. - Epigenetic mechanisms play an important role in learning and memory, and the study provides an overview of these mechanisms with a focus on the bidirectional relationship between the epigenome and the synapse.	(Campbell & Wood, 2019)
DNA methylation and its implications and accessibility for neuropsychiatric therapeutics.	DNA methylation control systems in the central nervous system are potential targets for novel treatments for learning and memory disorders.	- DNA methylation is a key epigenetic mechanism that regulates neuronal function and memory processes. - Neurons exhibit unique DNA methylation patterns, including non-CpG methylation and enrichment of 5-hydroxymethylcytosine, that are distinct from other cell types. - Current tools to manipulate DNA methylation lack the specificity and temporal control needed to fully understand its role in the brain, and new tools are required.	(Bredy, 2018)
The m6A-epitranscriptome in brain plasticity, learning and memory.	The m6A RNA modification regulates neuronal plasticity, learning and memory.	- The m6A epitranscriptome is an important regulator of neuronal plasticity, learning, and memory. - Disruptions to the m6A epitranscriptome are linked to various cognitive disorders in humans.	(Widagdo et al., 2022)

Experience-dependent neural plasticity, learning, and memory in the era of epitranscriptomics	Epitranscriptomic mechanisms, including RNA modifications, may play an important role in neural plasticity, learning, and memory.	• RNA modifications can influence various aspects of RNA function, including its structure, localization, and translation, which are important for neural plasticity and memory formation. • RNA modifications provide a rapid, context-dependent mechanism for regulating gene expression in neurons, without the need for signaling back to the nucleus. • Understanding the epitranscriptomic landscape of the brain will be crucial for elucidating the molecular mechanisms underlying learning and memory.	(Bredy, 2018)
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V. CONCLUSIONS

Epigenetic mechanisms including DNA methylation and histone modifications, play a ubiquitous role in learning and memory across different paradigms and brain regions. Epigenetic modifications are dynamically regulated in a temporally and spatially specific manner, with transient changes in the hippocampus supporting initial memory consolidation and persistent changes in the cortex supporting long-term memory maintenance. Epigenetic modifications are regulated by upstream signaling cascades, which establish precise "histone codes" that correspond to particular types of memory. The analysis results show that keywords that focus on learning appear eighty-one (81 times) with keywords Learning, Memory, Cognitive, Deep Learning. The contribution of molecular epigenetics in education such as 1) Understanding Genetics and Environment. 2) Learning about Development. 3) Ethics and Social Implications. 4) Development of Critical Thinking Skills.

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