

How Epigenetics Shapes Brain Diseases: Same Mechanisms, Different Outcomes

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LAY SUMMARY

Neurodegenerative diseases are conditions where nerve cells in the brain and the peripheral nervous system lose function over time, causing a decline in nervous system's physiological functions.

Epigenetics, alongside ageing and genetics (family history & mutations), have been recently found to have an important role in the cause of neurodegenerative diseases. Epigenetics are heritable changes in our gene expression that occur without altering the DNA sequence itself and dictate genes that will be turned on/off, ultimately impacting cellular processes that lead to these neurodegenerative diseases.

Fortunately, epigenetic changes are often times reversible, hence current researchers are urged to look for ways to target these epigenetic changes with drugs called epigenetic modulators, that can reverse destructive epigenetic marks and/or promote beneficial markers

This literature review focuses on how epigenetic mechanisms such as changes in DNA methylation, histone modification, and non-coding RNAs contribute to the onset and progression of Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease. It also highlights how emerging epigenetic therapies may offer new hope for treatment by restoring healthy gene expression patterns and could lead to new diagnostic tools (biomarkers) and more effective treatments for these debilitating diseases.

ABSTRACT

This report investigates the role of epigenetic mechanisms, like DNA methylation, histone methylation/acetylation, non-coding RNA changes, and microglial priming, in the pathogenesis of neurodegenerative diseases, specifically Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington's Disease (HD) 2. This report synthesizes findings from multiple primary research articles to analyze how these mechanisms influence gene expression across different diseases. Relevant primary research published between 2018 and 2024 was identified through searches on PubMed, ScienceDirect, and Google Scholar using predefined inclusion and exclusion criteria for studies examining epigenetic mechanisms in Alzheimer's, Parkinson's, and Huntington's diseases. Consistent patterns of hypermethylation were observed to silence genes critical for mitochondrial function, synaptic integrity, and neuroprotection. Histone modifications further contributed to inflammation and transcriptional dysregulation.¹ Notably, one counter-study revealed that hypomethylation and gene overexpression of synaptic transport genes in PD led to excitotoxicity, suggesting that epigenetic changes are not uniformly detrimental or beneficial.³ The direction and impact of such alterations are gene- and region-specific.⁸ These findings emphasize the complex, context-dependent nature of epigenetic dysregulation in neurodegeneration and highlight potential avenues for targeted therapeutic strategies.

Keywords: alzheimer's disease, parkinson's disease, huntington's disease, DNA methylation, histone modifications, chromatin remodeling

INTRODUCTION

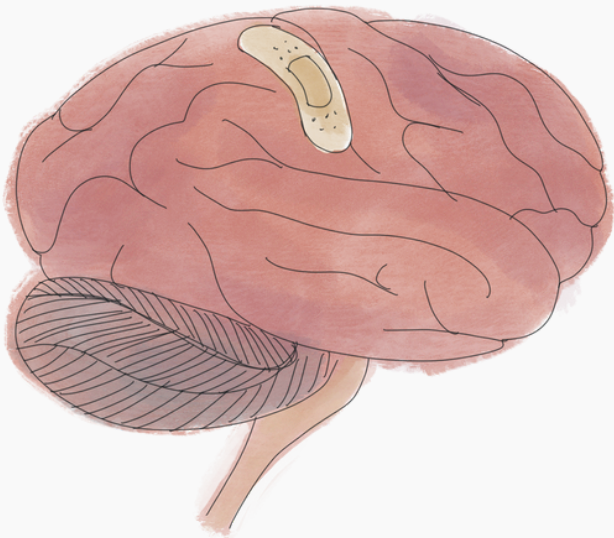
Neurodegenerative diseases are a major global health issue given their progressive neuronal loss and lack of curative treatments.⁹ Aging is the strongest risk factor for neurodegenerative disease, in part because it leads to cumulative dysregulation in gene expression.(Fan et al, 2024) This dysregulation in gene expression happens due to epigenetic modifications, such as **DNA methylation, histone modifications, and non-coding RNAs** (e.g., microRNAs, long noncoding RNAs).⁸ Unfavourable changes in gene expression due to harmful epigenetic modifications are closely linked to

be the primary causes of disease onset and heterogeneity and can be influenced by age, environmental exposures, and lifestyle.¹ Unlike permanent genetic mutations, epigenetic changes are reversible, offering potential targets for novel therapeutic interventions.⁵

Early studies have identified disease-specific epigenetic alterations: aberrant DNA methylation in APP and BACE1 promoters in Alzheimer's Disease (AD)², histone deacetylation changes linked to dopaminergic neuron vulnerability in Parkinson's Disease (PD)¹⁰, and altered histone methylation patterns in Huntington's Disease (HD) models.¹ Even more

compelling, non-coding RNAs such as microRNA-205 have emerged as potential modulators of disease-related gene expression (e.g., *LRRK2* in PD)¹². Yet, while extensive research exists individually for each mechanism or disease, an integrative review across these epigenetic layers and conditions is lacking.

This narrative literature review combines current research on how epigenetic modifications like **DNA methylation**, **histone modifications**, and **non-coding RNAs** contribute to AD, PD, and HD. By comparing these mechanisms across diseases, we aim to highlight shared and disease-specific epigenetic signatures and assess their potential as biomarkers or therapeutic targets.



METHODS

To answer the proposed research topic, I used a narrative analysis of existing primary research studies on the role of epigenetic mechanisms like DNA methylation, histone methylation/acetylation, and non-coding RNAs in the development of neurodegenerative diseases like AD, PD, and HD².

SEARCH STRATEGY:

Keywords: like alzheimer's disease, parkinson's disease, huntington's disease, DNA methylation, histone modifications, chromatin remodeling

Keywords were searched on platforms like Google Scholar, PubMed, and Science Direct to conduct a comprehensive research analysis.

Inclusion criteria for the article were:

- The article's content must focus on epigenetic mechanisms of Alzheimer's, Parkinson's or Huntington's Disease.
- Original peer-reviewed primary research, involving human, animal or in vitro models
- Article must have been published recently—within the years of 2018 and onwards

Exclusion criteria included:

- Review articles
- Papers that did not report original experimental data
- Studies focused exclusively on developmental disorders or cancer

Bias check and the quality of evidence

To reduce potential bias from research, studies chosen were

highly cited and influential academic publications. Since the analysis is a narrative review and not a systematic review, rigid protocols like PRISMA were not used, which could potentially skew the results as only studies with "significant findings" are more likely to be published, whereas those with "null" views are more likely not to be published. Hence, to address this, I used a critical appraisal approach to mitigate selection and interpretation bias⁷:

- Articles with clearly described methods, validated assays (e.g., ChIP-seq, qPCR), and statistically significant results ($p < 0.05$) were chosen⁷
- Reproducibility of results when cross-referencing from different studies to identify similar/different findings.⁷
- Recognized potential publication bias (i.e., favouring studies that report positive findings) and tried to include studies that acknowledge null or contradictory results.⁷

Furthermore, to strengthen the results from this narrative analysis, I included a **counterpoint study** that questions the **causality vs consequence** of histone modifications in PD, in order to showcase whether epigenetic changes are the disease drivers or the byproducts of the disease.

RESULTS

With the inclusion and exclusion criteria and specific keyword search, the following articles were chosen: see Table 1.

1. The role of histone methylation and heterochromatin remodelling in Neurodegeneration

According to Basavarajappa et al (2021) in the International Journal of Molecular Sciences, there was an imbalance in histone methyltransferases (HMTs) and histone demethylases (HDMs), which led to abnormal expression of genes governing synaptic plasticity and neuronal survival, in mouse models with Alzheimer's and Parkinson's Disease. Specifically, there was an increased expression of the gene **H3K9me2**—a repressive marker— in the hippocampus neurons.¹ This led to downregulation of memory-related genes in Alzheimer's disease.¹ Furthermore, in mouse models with Huntington's disease, overexpression of **SETDB1**, an H3K9 methyltransferase, led to heterochromatin loosening and silencing of transcription of genes involved in motor control¹ Furthermore, post-translational modifications in mouse models with Parkinson's led to heterochromatin disability as researchers found decreased H3K27me3, which is a trimethylation of lysine 27 on histone H3 (histone modification)¹, which is a repressive gene marker found at the promoter region of SNCA, potentially leading to disease pathogenesis.¹ Additionally, increased expression of H3K9ac was found, associated with increased neuroinflammation.¹ This was found through a ChIP-seq analysis in neuron chromatin obtained from brain tissue of mouse models with Huntington's Disease postmortem pre-frontal cortex and non-neurologic control systems.¹

[Figure 1¹] provides an illustration of histone methylation-specific epigenetic defects in neurodegenerative diseases.¹

2. DNA methylation and disease-specific gene silencing

Researchers, after analyzing DNA methylation patterns in the brain tissue of post-mortem humans, found huge amounts of methylation in the promoters of genes used for mitochondrial and synaptic functions, like PINK1, PRKN, and NDUFA2.⁸ The silencing of these genes is found to be associated with increased oxidative stress and loss of neurons related to dopamine.⁸

TABLE 1: SUMMARY OF PRIMARY RESEARCH ARTICLES INCLUDED IN THE NARRATIVE REVIEW EXAMINING EPIGENETIC MECHANISMS IN NEURODEGENERATIVE DISEASES

Author (Year)	Article Title (Shortened)	Disease Focus	Model System	Study Method	Country
Desplats et al. (2019)	Microglial memory of early-life stress	General (neurodegeneration risk)	Rat model	LPS exposure + ChIP-seq analysis	Argentina
Basavarajappa & Subbanna (2021)	Histone methylation, regulation pathways in neurodegenerative diseases	AD, PD, HD	Mouse model	HMT/HDM assays + gene expression	USA
Klokkaris & Migdalska-Richards (2024)	Epigenetic changes in PD brain	Parkinson's disease	Human post-mortem tissue	DNA methylation profiling	UK
Fisher & Torrente (2024)	Histone PTMs & heterochromatin remodeling	AD, PD	Human + cell culture	Histone modification mapping + immunoblot	USA

(LPS = LIPOPOLYSACCHARIDE; PTMS = POST-TRANSLATIONAL MODIFICATIONS; HMT = HISTONE METHYLTRANSFERASE; HDM = HISTONE DEMETHYLASE)

Similarly, previous studies showed that methylation of BACE1 (an enzyme important in the formation of myelin sheaths in peripheral nerve cells) and APP promoters in Alzheimer's models reduces their gene expression initially, but fluctuates with disease progression.²

3. Microglial memory and epigenetic priming via early-life stress

Early-life stress induces long-lasting epigenetic changes in microglial cells due to a concept called microglial memory, as rat models in the experiment showed that early exposure to lipopolysaccharide (LPS) led to upregulation of inflammatory genes (e.g., interleukin-1 beta, tumor necrosis factor alpha) upon secondary stimulation, even months later.³ This was associated with stable changes in histone marks (H3K4me3, H3K27ac) in gene promoter regions, priming microglia for a hyper-responsive state in adulthood.³ Genes exposed to stress early on in one's life led to microglial memory, which made them hypersensitive to stress later on in adulthood, which made the brain more prone to neurodegeneration.³

4. Non-coding RNAs in disease-specific gene regulation

MicroRNAs (miRNAs) also play an important role in regulating Parkinson's Disease-associated genes, as downregulation of a short RNA molecule, miR-205 leads to failure in suppressing LRRK2, a gene mutated found in PD patients.⁸ Additionally, downregulation of miR-124 has been shown to impair neuronal differentiation and reduce synaptic plasticity by decreasing the expression of neurogenic transcription factors

such as REST and CREB, leading to disrupted axonal growth and altered synapse formation.⁸ These changes in miRNA levels were directly linked to neurodegenerative phenotypes in PD cell models, suggesting non-coding RNAs act as post-transcriptional regulators in neurodegeneration.⁵ This mechanism is critical for fine-tuning the expression of genes such as LRRK2 and other PD-related targets, and its disruption contributes to abnormal protein accumulation and neuronal vulnerability.⁴ While Desplats et al. emphasised neuroinflammation as a driving factor, the study also proved that the inflammatory state arises from epigenetic priming.³ While Desplats et al. emphasised neuroinflammation as a driving factor, the study also proved that the inflammatory state arises from epigenetic priming.³ [Figure 2] illustrates how a miRNA binds to the 3'UTR of a target mRNA.

Discussion – implications, comparisons, limitations, future research

This narrative literature analysis conducted a thorough investigation of various primary research articles to analyze how epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, contribute to the development and progression of AD, PD, and HD. A common trend existed among all studies: epigenetic dysregulation leads to altered expression of genes that code for synaptic plasticity, neuroinflammation, and mitochondrial function—all markers of neurodegeneration^{1,3,5,8}

TABLE 2. SUMMARY OF EPIGENETIC FACTORS AND THEIR EFFECTS ON ENZYME ACTIVITY, GENE EXPRESSION, AND BRAIN REGIONS ACROSS NEURODEGENERATIVE DISEASE MODELS.

Disease	Epigenetic factor	Enzyme / mRNA affected	Gene(s) affected	Model System	Brain Region Affect	Effect
AD	Histone methylation	G9a/GLP1	Gria2, Grin2b, Shank21	FAD mice1	Pre-frontal cortex, hippocampus1	↑ H3K9me2 → Gene repression1
AD	Histone methylation	KMT2A-D1	Ankyrin 11	Post-mortem human1	Pre-frontal cortex- Nucleus 1	↑ H3K4me3 → Gene activation1
AD	Histone methylation	-	-	CK-p25 Alzheimer's transgenic mouse model1	IncRNA targets1	↑ H3K4me3, ↓ H3K27me31
PD	Histone Modification	-	Immune-response genes 5	Human PD cortex5	Substantia Nigra / general5	↑ H3K9ac → Inflammation 5
PD	Histone Modification	-	LRRK25	Human PD tissue / in vitro 5	-	↓ H3K27me3 → Genomic instability 5
PD	Non-coding RNA	miR-2055	LRRK25	Human PD / in vitro 5	-	↓ miR-205 → ↑ LRRK2 5
PD	Non-coding RNA	miR-1245	Neuronal genes5	PD cell models5	-	Dysregulated expression5
PD	DNA Methylation	-	PINK1, PRKN, ATP13A2, NDUFA28	Human PD brains 8	Substantia nigra pars compacta8	↑ Methylation → ↓ expression8
General	Histone Acetylation	-	IL-1β, TNF-α3	LPS-exposed rats3	Microglia 3	↑ H3K4me3, H3K27ac → Inflammatory priming 3

Abbreviations:

↑ = increased; ↓ = decreased; → = leads to; - = not specified, AD: Alzheimer's Disease , ATP13A2: ATPase cation transporting 13A2, FAD: Familial Alzheimer's Disease mouse model , Gria2/ Grin2b: Glutamate ionotropic receptor AMPA type subunit 2/2B, G9a/GLP: Euchromatic histone lysine methyltransferases , H3K4me3: Histone 3 lysine 4 trimethylation , H3K9me2/3: Histone 3 lysine 9 di/trimethylation , H3K27me3: Histone 3 lysine 27 trimethylation , LPS: Lipopolysaccharide (inflammation inducer), LRRK2: Leucine-rich repeat kinase 2, miR-205, miR-124: microRNAs , NDUFA2: NADH:Ubiquinone Oxidoreductase Subunit A2 (a protein coding gene), PINK1: PTEN-induced kinase 1, PRKN: parkin, PD: Parkinson's Disease , Shank2: SH3 and multiple ankyrin repeat domains 2, SNCA: α-synuclein.

Across all the studies, histone methylation was found to be important for controlling gene expression of genes for major neuronal function ^{1,3,5,8}. The study found that elevated H3K9me2 and reduced H3K27me3 in Alzheimer's and Parkinson's models, correlated with suppression of synaptic plasticity-related genes and inflammatory signalling.⁵ Furthermore, Table 1 depicts how overexpression of SETDB1, and other histone methyltransferases resulted in chromatin compaction and motor gene transcriptional repression in Huntington's Disease, which underlies motor dysregulation seen in HD models.¹ These findings suggest that histone marks disrupt transcriptional homeostasis and trigger disease phenotypes. Correspondingly, post-mortem PD brain DNA methylation profiles suggested hypermethylation of protective genes like PINK1 and PRKN, which in turn hinted at gene silencing in mitochondrial pathology and degeneration of dopaminergic neurons.¹

Non-coding RNAs were also shown to be critical epigenetic regulators. Downregulation of the miR-205 that suppresses LRRK2 and dysregulation of miR-124, a neuronal differentiation regulator, were shown to exacerbate PD pathology.⁵ This supports the claim that epigenetic changes are not just consequences of disease but may also act as initiating factors—highlighting the need to interpret inflammation in the context of upstream regulatory changes. Microglial priming by early-life stress also illustrates how lasting histone acetylation marks like H3K4me3 can lead to increased neuroinflammation in later life, providing evidence for the hypothesis that epigenetic memory plays a role in long-term brain health.³ These findings suggest that early environmental exposures can prime the brain for future neurodegeneration via long-term epigenetic reprogramming.³

TABLE 2. SUMMARY OF EPIGENETIC FACTORS AND THEIR EFFECTS ON ENZYME ACTIVITY, GENE EXPRESSION, AND BRAIN REGIONS ACROSS NEURODEGENERATIVE DISEASE MODELS.

Epigenetic Mechanism	Disease	Key Findings
Histone methylation	AD, HD, PD	Alters synaptic genes, promotes inflammation, disrupts chromatin structure
DNA methylation	AD, PD	Silences mitochondrial, synaptic, and neuroprotective genes
Histone acetylation	PD	Deregulates immune-related transcription
Non-coding RNAs (miRNAs)	PD	Loss of gene repression (e.g., LRRK2) contributing to proteinopathy
Microglial priming	General Findings	Epigenetic marks from early-life stress predispose to exaggerated inflammation

Abbreviations

AD: Alzheimer’s Disease , HD: Huntington’s Disease, LRRK2: Leucine-rich repeat kinase 2 , miRNA: microRNA, PD: Parkinson’s Disease

COUNTER-STUDY

However, one of the studies by Klokkaris and Migdalska-Richards (2024) offered a critical counterpoint to the dominant epigenetic narrative observed in other studies by emphasizing disease- and gene-specific variability in DNA methylation patterns.⁸ While other studies emphasize how epigenetic DNA hypermethylation is a primary mechanism of silencing genes involved in neuroprotection, metabolism, and synaptic maintenance, Klokkaris and Migdalska-Richards’ analysis of postmortem substantia nigra samples from Parkinson’s Disease (PD) patients revealed a completely different trend⁸. They found that genes involved in synaptic vesicle cycling and glutamatergic neurotransmission were hypomethylated and subsequently overexpressed.⁸ This resulted in increased excitatory signalling and a heightened risk for glutamate-induced excitotoxicity, which is a common contributor to neuronal death in PD8.

This insight complicates the most common assumption that methylation acts solely as a silencing force in neurodegenerative disorders. This insight rather showcases the idea that the epigenetic change will have context-dependent functional changes, determined by both the biological role of the gene affected and the neural circuit in which it is expressed. For instance, while hypermethylation of mitochondrial or antioxidant genes may impair neuronal resilience, hypomethylation of genes that drive excitatory neurotransmission may intensify neurotoxicity. Therefore, a deeper analysis on the counter study shows that inflammation happens due to epigenetics. This showcases that epigenetic mechanisms increase disease onset and factors that in a positive feedback way, also increase disease progression.

A summary of epigenetic mechanisms that lead to the onset & progression of PD have been summarized in Figure 3.⁸

Significance to the research field:

These findings showcase the central role of epigenetic modifications in both initiating and perpetuating neurodegenerative processes. Unlike genetic mutations, epigenetic changes are reversible, making them attractive targets for therapeutic intervention.¹¹ For instance, histone deacetylase inhibitors or DNA methyltransferase inhibitors could restore normal gene expression patterns.⁴ Moreover, miRNAs may serve as diagnostic biomarkers and therapeutic agents by modulating disease-related genes.⁸ This review adds value by comparing multiple epigenetic layers across three neurodegenerative diseases, highlighting both shared and disease-specific regulatory mechanisms. Such integrative insights are crucial for developing precision epigenetic therapies and early detection biomarkers.

Limitations:

As a narrative review, this study is limited by selection and interpretation bias. Only articles published after 2018 and with significant findings were included, which may exclude important null results. The absence of PRISMA guidelines means the methodology lacks the rigour of a systematic review. Additionally, most studies analyzed were conducted in animal models or cell lines, which may not fully recapitulate human neurodegeneration. Furthermore, the functional significance of some gene expression changes remains unclear—especially in cases where gene function was not specified, or where it was not evident whether increased or decreased expression was beneficial or detrimental for the disease.

Summary of Discussion

Table 2 offers a useful summary of the directionality of gene expression changes in response to DNA methylation across neurodegenerative diseases. Notably, it shows that Parkinson’s Disease exhibited the most balanced profile, with an almost equal number of hypomethylated/overexpressed

and hypermethylated/underexpressed genes, suggesting complex and competing epigenetic forces at play. In contrast, AD had a larger proportion of hypermethylation-linked downregulation, particularly in genes related to synaptic plasticity and glucose metabolism. These observations support the hypothesis that while epigenetic dysregulation is a shared feature across neurodegenerative disorders, the exact methylation patterns and their consequences on gene expression differ depending on the disease type, brain region, and molecular pathway involved.

Conclusion

This review addressed the role of epigenetic regulation in neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's. The aim was to have an understanding of the role of gene expression alteration in disease pathogenesis. Four principal articles between 2018–2024 were selected via ScienceDirect, MDPI, and Frontiers^{1,3,5,8}. Studies included focused on gene-level epigenetic changes in human brain tissue or disease models. Data was analyzed for patterns of DNA methylation, histone modifications, and non-coding RNA expression^{1,3,5,8}. Hyper-methylation of neuroprotective genes and disrupted histone marks between studies were linked to inflammation, mitochondrial dysfunction, and protein misfolding². For example, miRNA dysregulation (e.g., miR-7, miR-153) was observed to influence PD-related protein aggregation⁵. Gene expression patterns inevitably showed inflammatory markers overexpression and protective mechanism suppression⁵. However, a counter-study showed that hypomethylation of excitatory genes in PD can also lead to harmful consequences, unveiling the complex, context-specific nature of epigenetic modification⁸.

Acknowledgements

Special thanks to the authors of the primary research studies referenced, whose work provided critical insight into the epigenetic mechanisms underlying neurodegenerative diseases.

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Figures/Illustrations

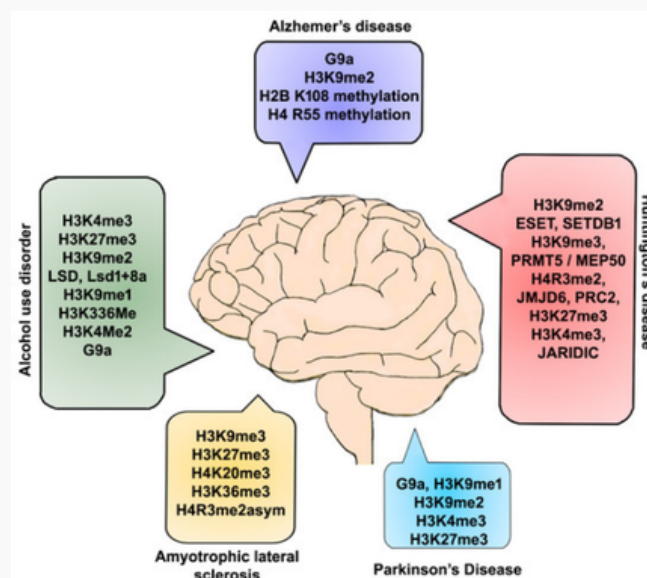


Figure 1²: Neurodiverse-inducing conditions have been shown to affect DNA-associated histone methylation via specific Lysine Methyltransferases and KDMs Lysine Demethylases, followed by several changes in gene and protein expression that are important for cognitive and other ND-related brain pathologies.²

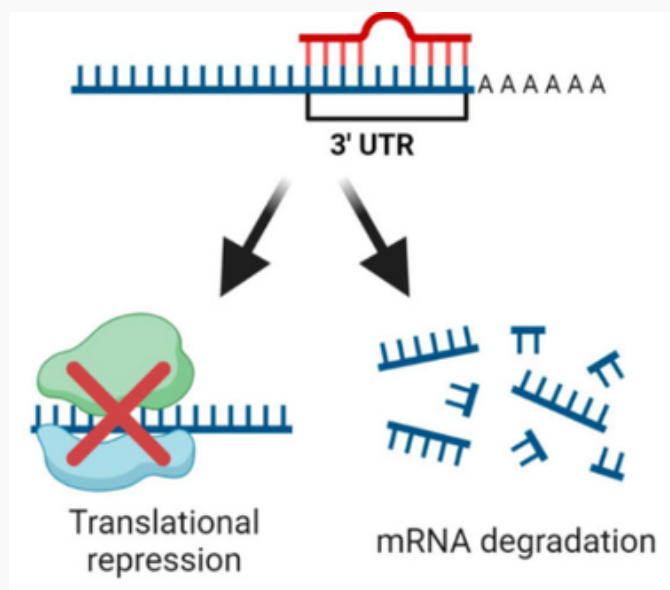


Figure 2³: Illustration showing how a miRNA binds to the 3'UTR of a target mRNA, which results in gene silencing either by translational repression or mRNA degradation.³

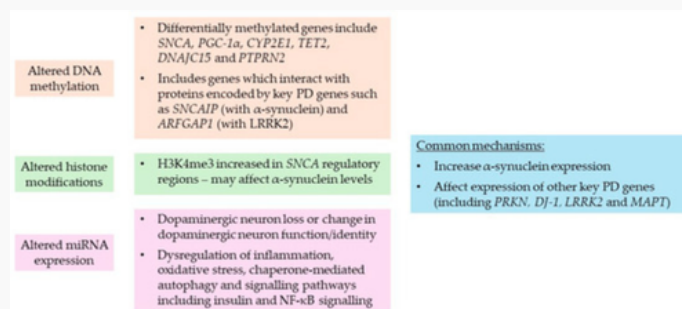


Figure 3³: Studies related all three epigenetic mechanisms to an increase in α -synuclein expression and changes in multiple PD risk gene expression levels.