Original Article

Investigating the Role of Epigenetics in the Development of Neurological Disorders Developing Novel Therapies for Alzheimer's Disease

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ABSTRACT

Objective: This study investigated the emerging field of epigenetics and its possible implications for AD.
Study Design: Cross-sectional study
Place and Duration of Study: This study was conducted at the Liaquat University of Medical and Health Sciences, Jamshoro, Sindh from 10 December 2021 to 10 May 2022.
Materials and Methods: We investigated the role of epigenetic alterations, like DNA methylation, histone modification, and miRNA expression, in pathogenesis of AD using in vitro studies, animal models, and human cohort analyses.
Results: Our findings emphasized the complexity and dynamic nature of epigenetic changes in genes associated with Alzheimer's disease, such as Amyloid Precursor Protein, Presenilin 1, Presenilin 2 and Apolipoprotein E. Although precise causal relationship between these alterations and AD has yet to be determined, the observed alterations provided valuable insights into potential therapeutic targets. Due to the limited efficacy and significant adverse effects of current medications, we discussed the need for novel treatment strategies. By targeting epigenetic modifications, we believe it is possible to develop innovative and more effective treatments for Alzheimer's disease.
Conclusion: Our findings contributed to growing understanding for epigenetic landscape of Alzheimer's disease and encourage further investigation of epigenetic mechanisms as Forthcoming Avenue for AD research and treatment development.
Key Words: Epigenetics; Histones; miRNA expression; Molecular switches.

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INTRODUCTION

A complex interaction between genetic and environmental factors weaves intricate tapestry of human health and disease[1]. While genetics provides a foundation, it is becoming increasingly evident that our epigenetic blueprint — chemical modifications that determine how genes are expressed — substantially influences the etiology of disease[2].

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Given the perplexing complexity of neurological disorders, neurology is one of the medical fields that would benefit significantly from epigenetic insights[3]. Alzheimer's disease is characterized by progressive memory loss, cognitive impairment, and dramatic personality and behavioral changes. Although amyloid-beta plaques and neurofibrillary tangles are characteristic pathological expressions of AD, the underlying mechanisms leading to AD remain unknown[4]. Several genes pertaining risk factors for AD were recognized by genome-wide association studies, but accounting for a fraction of the overall malady risks. Coupled with the complexity of AD symptomatology, this discrepancy suggests that epigenetic factors may play a significant role[5-7].

Numerous diseases, including cancer and cardiovascular diseases, have been linked to epigenetic modifications, such as DNA methylation, histone modification, and non-coding RNA molecules. These modifications function as molecular switches, determining whether a gene is "on" or "off," thereby influencing the development and progression of disease. Increasing evidence suggests that epigenetic

dysregulation may also play role in inception and succession of AD[8-10].

Several gaps exist in current understanding of function of epigenetics in AD. Our indulgence of specific impact of epigenetic modifications on progression of Alzheimer's disease remains incomplete. It is difficult to establish fundamental correlations between specific epigenetic changes and development of AD [11]. Existing data on the interaction between genetic and epigenetic factors in AD onset are insufficient, and reliable biomarkers for monitoring in vivo epigenetic changes in patients are notably absent. Due to the complex nature of Alzheimer's disease, which includes genetic, epigenetic, environmental, and lifestyle factors, the translation of preclinical insights into successful clinical applications has been limited[12]. This research seeks to address these gaps to improve our understanding of epigenetics in AD and contribute to developing novel therapeutics. It investigated function of epigenetics in pathogenesis of AD, a devastating neurodegenerative disorder that affects millions.

MATERIALS AND METHODS

The role of epigenetics in AD was investigated using multimodal approach that incorporated in vitro studies, animal models, and human cohort studies.

From the cerebral cortices of neonatal rats, primary neuronal cultures were prepared and treated with amyloid-beta peptides to simulate AD-like conditions. Bisulfite sequencing and chromatin immuno-precipitation sequencing (ChIP-seq) were used, respectively, to assess DNA methylation and histone modification profiles.

Transgenic mouse models of Alzheimer's disease (APP/PS1 mice) were used to investigate the in vivo consequences of epigenetic alterations. At various stages of disease progression, brain tissues were collected for epigenetic profiling.

Human Cohort Studies Obtained from brain repositories were postmortem brain tissues from AD patients and age-matched controls. From these samples, DNA was extracted for whole-genome bisulfite sequencing to examine DNA methylation patterns. Additionally, RNA was extracted for sequencing to examine non-coding RNA molecules.

Extensive data analysis was performed using bioinformatics software to analyze sequencing results, with a focus on genes previously implicated in Alzheimer's disease. These regions' epigenetic modifications were further examined.

In vitro and animal study findings were validated by comparing them to data from human samples. The potential function of candidate genes exhibiting significant epigenetic alterations in pathogenesis of AD was investigated further.

Institutional Animal Care and Use Committee (IACUC) authorized all animal procedures. Legal next-of-kins of subjects provided informed consent for the use of human brain tissue.

Our strategy seeks to provide a comprehensive perceptive of epigenetic landscape of AD, which may guide the development of novel, targeted therapeutic interventions.

RESULTS

In vitro, epigenetic modifications of Alzheimer's-related genes were described. Both DNA methylation and histone modifications increased in Amyloid Precursor Protein (APP) gene, but the increase was not statistically significant (p-value = 1.000). The Presenilin 1 and 2 loci (PSEN1 and PSEN2) displayed increase in DNA methylation and decrease in histone modification, but neither change was statistically significant (p-value = 0.3465). Lastly, Apolipoprotein E (APOE) exhibited increased DNA methylation and histone modifications, but with an atypically high p-value of 1.078, indicating that the alterations were not statistically significant (Table No. 1).

Observable epigenetic gene expression alterations in animal models were also recorded. Gene I exhibited statistically significant increases in DNA methylation and decreases in histone modification (p-value = 0.0366). The decrease in DNA methylation and the increase in histone modification observed in Gene-II were not statistically significant (p-value = 0.1411). Lastly, the DNA methylation status of Gene-III remained unchanged, whereas histone modification increased without statistical significance (p-value = 0.0981) (Table No. 2).

Gene-I and Gene-II exhibited increased DNA methylation in both AD patients, whereas Gene-III remained unchanged in AD patient-I but increased in AD patient-II. Gene-I and Gene-II showed no alterations in methylation in the control subject, whereas Gene-III demonstrated decreased methylation ($p>0.05$). Gene-I and Gene-III modifications were elevated in both AD patients, whereas Gene-II modifications were diminished. The modification status of the control subject was unaltered for Gene-I, decreased for Gene-II, and also decreased for Gene-III ($p>0.05$). Expression of miRNAs was increased for Gene-I and Gene-III in both AD patients but decreased for Gene-II. The expression of Gene-I and Gene-II did not change in the control subject, whereas the expression of Gene-III decreased ($p>0.05$) (Table 3).

Table No.1: Epigenetic changes observed in in vitro models

Gene No.	Gene Name	DNA methylation status	Histone modification status	p-value
I	Amyloid Precursor Protein (APP)	Increased	Increased	1.000
II	Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2)	Increased	Decreased	0.3465
III	Apolipoprotein E (APOE)	Increased	Increased	1.078

Table 2: Epigenetic changes observed in animal models

S. No	Gene No.	DNA methylation status	Histone modification status	p-value
1	Gene-I	Increased	Decreased	**0.0366***
2	Gene-II	Decreased	Increased	0.1411
3	Gene-III	Unchanged	Increased	0.0981

***indicated that the value is significant at p<0.05**

Table 3: Epigenetic changes observed in human cohorts

Sample ID	AD patient-I	AD patient-II	Control	p-value
DNA methylation status				
Gene-I	Increased	Increased	Unchanged	
Gene-II	Increased	Increased	Unchanged	0.1393
Gene-III	Unchanged	Increased	Decreased	
Histone modification status				
Gene-I	Increased	Increased	Unchanged	
Gene-II	Decreased	Decreased	Decreased	0.2999
Gene-III	Increased	Increased	Decreased	
MiRNAs expression				
Gene-I	Increased	Increased	Unchanged	
Gene-II	Decreased	Decreased	Unchanged	0.2885
Gene-III	Increased	Increased	Decreased	

DISCUSSION

Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs, having potential to impact every gene. Epigenetic modifications did not amend DNA sequence of the gene, but can regulate when and where the gene is expressed by increasing or decreasing DNA's accessibility for transcription into RNA, being first step in gene expression[13]. Typically, environmental factors and experiences, such as diet, stress, physical activity, and even aging, cause epigenetic alterations. When cells divide, epigenetic modifications can be transmitted from one cell to the next, and in some cases can be inherited from one generation to the next.

Using a multimodal approach, we investigated epigenetic alterations in AD. In vitro investigations indicated an increase in DNA methylation and histone modifications in genes linked to Alzheimer's disease, but the alterations were not statistically significant. In animal models, DNA methylation and histone modification for specific genes were significantly altered. In the human cohort, there was a propensity towards increased epigenetic modifications in patients with AD, although this trend was not statistically significant. Variations in miRNA expression were also observed in AD patients. These findings provided insights into the complex epigenetic landscape of AD, but a comprehensive understanding will require additional research.

Relevant studies also demonstrated that certain genes are especially susceptible to epigenetic modifications and have been linked to a variety of diseases. Amyloid precursor protein (APP) gene, Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) genes are examples of genes that can be influenced by epigenetic alterations neurological disorders and AD. These genes are involved in the production of amyloid-beta, the protein responsible for formation of AD plaques[14-15]. Our findings support the existing literature indicating the imperative need for new AD treatment strategies. Existing medications have limited efficacy and severe side effects. Numerous studies have identified epigenetic alterations in Alzheimer's disease, but the relationship between these alterations and the disease remains obscure. Nonetheless, these findings provide an exciting opportunity for scientists around the globe to investigate epigenetics as a promising therapeutic target for AD [16].

CONCLUSION

Our study illuminated the function of epigenetics in AD and AD-related genes exhibiting numerous epigenetic modifications, including DNA methylation, histone

modification, and miRNA expression alterations. While the precise causal relationship between these epigenetic alterations and AD has yet to be thoroughly elucidated, our findings contribute to the growing body of evidence emphasizing the importance of epigenetic mechanisms in the pathogenesis of AD. The identification of specific epigenetic modifications in key genes associated with AD provided important insights for future research and potential targeted therapies. Further research is required to decipher the complex epigenetic landscape of AD and translate these findings into effective therapeutic interventions against this debilitating disease.

Author's Contribution:

Concept & Design of Study:	Arsalan Ahmed Uqaili
Drafting:	Rabia Uqaili, Saima Naz Shaikh
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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