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CRISPR- based epigenetic editing: A new era of disease control without gen, A review

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Abstract

CRISPR-based epigenetic editing is a revolutionary technique that enables precise control of gene expression without altering the underlying DNA sequence. This approach uses a modified CRISPR/Cas9 system, where the nuclease activity of Cas9 is inactivated (dCas9) and fused with epigenetic effector proteins to modify chromatin structure or DNA methylation at specific genomic loci. By targeting regulatory regions of genes, this method allows for activation or repression of gene function in a reversible and controlled manner. Unlike traditional genome editing, which involves permanent changes in DNA, epigenetic editing offers a safer and more flexible alternative for therapeutic interventions.

This project focuses on the principles, mechanisms, and applications of CRISPR-based epigenetic editing in disease control. It highlights its potential in treating complex conditions such as cancer, neurological disorders, cardiovascular diseases, and metabolic syndromes, where abnormal gene expression plays a key role. The technology's non-permanent nature, high specificity, and adaptability make it an essential tool in modern biotechnology and personalized medicine. By providing a deeper understanding of its advantages, challenges, and future prospects, this study emphasizes CRISPR-based epigenetic editing as a promising approach for next-generation therapies.

Keywords: CRISPR; Epigenetic Editing; dCas9; Gene Regulation; DNA Methylation; Histone

1. Introduction

- CRISPR – Clustered Regularly Interspaced Short Palindromic Repeats
- Clustered: The DNA sequences are grouped together
- Regularly Interspaced: There are equal spaces between the sequences
- Short: Each sequence is short in length
- Palindromic: The DNA reads the same forwards and backwards — like the word "level"

1.1. CRISPR-Based Epigenetic Editing

CRISPR-based epigenetic editing is a specialized variation of CRISPR technology in which a catalytically inactive Cas9 (dCas9) is fused to epigenetic effector proteins. Instead of cutting DNA, this modified complex binds to a target gene and alters its epigenetic state— for example, by adding or removing chemical tags like methyl groups or acetyl groups from histones or DNA. These changes can activate or silence genes without permanently altering the underlying genetic code.

This approach is different from conventional gene editing because:

- It is reversible — the modifications can be undone if the epigenetic marks are later removed.
- It preserves genomic integrity — the DNA sequence remains unchanged.
- It offers fine-tuned control — the level and duration of gene activity can be regulated.

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Example in Action:

- Using dCas9-p300 to add acetyl groups to histones near a gene promoter → Gene becomes more active.
- Using dCas9-DNMT3A to add methyl groups to DNA at a promoter → Gene becomes silenced.

1.2. Purpose of CRISPR-Based Epigenetic Editing

CRISPR-based epigenetic editing has emerged as one of the most promising tools in modern molecular biology, designed to achieve precise and reversible control of gene activity without altering the underlying DNA sequence. Unlike conventional CRISPR-Cas9 systems, which create double-strand breaks in DNA to edit genes permanently, this approach uses a modified form of the Cas9 protein, known as deactivated Cas9 (dCas9). While dCas9 loses its cutting ability, it still retains its capacity to be guided by a synthetic RNA molecule—known as a guide RNA (gRNA)—to a specific DNA sequence. Once positioned, dCas9 is fused to epigenetic effector proteins such as DNA methyltransferases (DNMT3A), histone acetyltransferases (p300), or demethylases (TET1). These effector proteins can add or remove chemical modifications on DNA or histone proteins, thereby switching genes on or off as required.

The primary purpose of CRISPR-based epigenetic editing is to correct abnormal gene expression patterns that contribute to disease. Many disorders—such as cancer, neurodegenerative diseases, metabolic syndromes, and autoimmune conditions—are not caused by mutations in the DNA sequence itself but by epigenetic changes that alter how genes are expressed. This technology enables scientists to directly target those epigenetic marks, reversing harmful changes or restoring beneficial ones. Because the underlying DNA remains untouched, the process is considered safer and potentially more acceptable in clinical applications compared to permanent genome editing.

Another major purpose lies in therapeutic applications. In oncology, for example, CRISPR- based epigenetic editing could be used to silence oncogenes—genes that drive cancer development—or to reactivate tumor suppressor genes that have been switched off by DNA methylation. In neurodegenerative diseases such as Alzheimer's and Parkinson's, it could be applied to restore the expression of protective genes that help maintain neuronal health. In metabolic disorders like diabetes, it could help normalize the expression of genes involved in insulin production and glucose metabolism. These strategies offer the possibility of treating diseases at their root cause, rather than merely addressing symptoms.

In summary, the purpose of CRISPR-based epigenetic editing is multi-dimensional:

- Medical treatment of diseases driven by abnormal gene expression.
- Scientific discovery through precise, reversible gene control.
- Agricultural improvement without introducing foreign DNA.
- Advancement of personalized medicine tailored to individual epigenetic profiles.
- Ethical and regulatory benefits compared to permanent genome editing.

Through these diverse applications, CRISPR-based epigenetic editing is poised to become a key technology in the next era of biotechnology, offering precision, flexibility, and safety in both research and real-world applications.

2. Gene modification

2.1. Gene

A gene is a small section of DNA that carries the instructions to make specific proteins, which are the building blocks and workers of the body. Genes are found inside almost every cell, and they control how the body grows, functions, and responds to the environment.

Genes are the basic physical and functional units of heredity. They are made up of DNA and act as instructions to make molecules, most often proteins that are essential for life. Genes determine traits such as eye color, blood type, height, and even influence behavior and disease risk. Without genes, cells would have no instructions to grow, repair, or reproduce.

2.1.1. Example genes:

- BRCA1 → helps repair DNA damage (mutations can lead to cancer risk).
- HBB → makes hemoglobin for carrying oxygen in blood.
- TP53 → tumor suppressor gene, prevents uncontrolled cell growth.

2.2. Structure of a Gene

- Genes are not just continuous strings of information — they have distinct regions:
- Promoter region → controls when and how much a gene is expressed.
- Exons → coding sequences that are translated into proteins.
- Introns → non-coding sequences removed during RNA processing.
- Terminator sequence → signals the end of transcription.

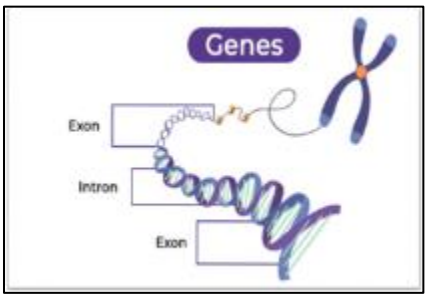

Figure 1 Structure of Gene

2.3. Functions of Genes

Genes are the molecular units of heredity that carry instructions for building and maintaining the life of an organism. They act like blueprints stored in DNA, guiding cells on what to produce, when to produce it, and in what quantity. The functions of genes are diverse, as they are responsible for everything from basic cellular activities to complex traits in living organisms. Below are the major functions:

Protein Coding, Regulation of Gene Activity, Enzyme Production, Structural Support, Cell Communication, Defense and Immunity, Transmission of Hereditary Information, Metabolic Control, Cell Growth and Differentiation, Adaptation and Evolution, Location and Organization

2.4. The Central Dogma

The process of gene expression follows three main steps:

- Replication → DNA is copied during cell division.
- Transcription → DNA is transcribed into messenger RNA (mRNA).
- Translation → mRNA is translated into a protein sequence.

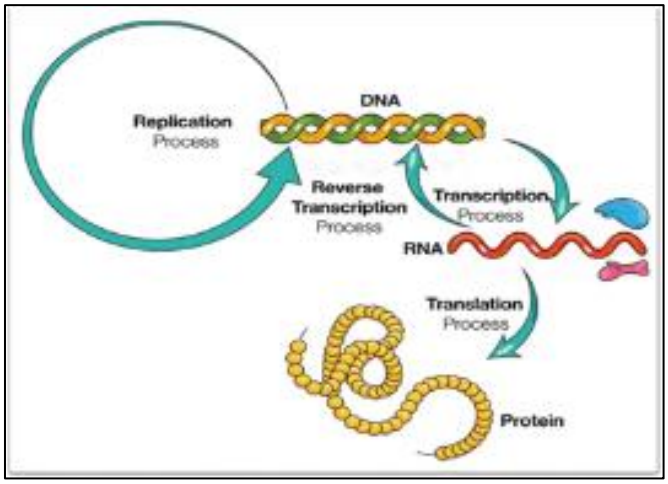

Figure 2 The Central Dogma of Biology: DNA replicates to preserve genetic information, transcribes into mRNA to carry the genetic code, and translates into proteins that perform essential cellular functions

2.5. Genes and Genetic Variation

Genes exist in different versions called alleles. These variations are why humans have unique appearances and traits. Some variations are harmless, while others can increase the risk of diseases such as cystic fibrosis, sickle cell anemia, or certain cancers.

2.6. The Role of Genes in Evolution

Over generations, mutations in genes can accumulate and lead to the development of new traits. This genetic diversity is the raw material for evolution, allowing species to adapt to changing environments.

2.7. Genes and Epigenetics

Not all genes are active at all times. Cells use epigenetic mechanisms — chemical modifications like DNA methylation or histone acetylation — to turn genes on or off without changing the actual DNA sequence. Epigenetic control is crucial for development, learning, and disease prevention.

2.8. Gene modification:-

Gene modification, also called genetic engineering or genome modification, refers to the intentional alteration of an organism's genetic material to achieve desired characteristics.

This can involve:

- Adding a gene from another species (transgenesis).
- Removing or disabling an existing gene (gene knockout).
- Correcting faulty genetic sequences (gene therapy).
- Regulating how strongly or weakly a gene is expressed (epigenome editing).

2.9. Types of Gene Modification

- Gene Editing (A Precise Subset of Gene Modification)
- Gene editing changes DNA at specific locations, often by cutting and replacing targeted sequences.

It is the most precise and controlled form of gene modification.

- Key Gene Editing Tools:
  - CRISPR-Cas Systems – Guide RNA directs the Cas enzyme to a DNA site, where it cuts and allows changes. Variants like Cas12 and Cas13 target different molecules (DNA vs. RNA).
  - Prime Editing – Works like a DNA "search-and-replace," allowing insertion, deletion, or substitution without cutting both DNA strands.
  - Base Editing – Alters a single base (A, T, C, G) without breaking the DNA.
  - TALENs – Proteins engineered to bind and cut DNA precisely.
  - Zinc Finger Nucleases (ZFNs) – Early protein-based DNA cutters.
- Other Gene Modification Methods
  - Gene Insertion via Viral Vectors – Harmless viruses deliver new genetic material into cells.
  - RNA Interference (RNAi) – Silences specific genes temporarily.
  - Epigenome Editing – Uses dCas9 or other proteins to turn genes on or off without changing the DNA sequence.
  - Recombineering – A bacterial engineering method for large DNA constructs.

- **Step-by-Step Process of Gene Modification**
  - Identify the Target Gene – Locate the gene linked to the desired or undesired trait.
  - Select the Technique – Choose between gene editing, gene insertion, silencing, or epigenome editing.
  - Design the Editing Tool – Create guide RNA or engineer a protein (TALEN/ZFN).
  - Deliver the Tool – Use viral vectors, lipid nanoparticles, electroporation, or microinjection.
  - Modify the DNA/RNA – Make precise changes to the target sequence.
  - Cell Repair/Integration – The cell's repair system incorporates the new sequence.
  - Verification – Genetic sequencing confirms the change.
  - Testing & Application – Modified organism is tested for safety and effectiveness.

Applications

- Gene Therapy – Treating inherited disorders (e.g., sickle cell anemia, cystic fibrosis).
- Cancer Immunotherapy – Editing immune cells (CAR-T) to target tumors.
- Infectious Diseases – Removing viral DNA from infected cells (HIV research).
- Rare Disease Treatments – Clinical trials using CRISPR for muscular dystrophy and retinal diseases.

3. CRISPR

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. It was first discovered in bacteria as a natural defense system. When a virus attacks, bacteria use CRISPR with a helper protein called Cas9 to cut and destroy the virus's DNA. Later, scientists turned this system into a tool called CRISPR-Cas9, which works like molecular scissors. It can cut specific parts of DNA to help fix or remove faulty genes in humans, animals, or plants.

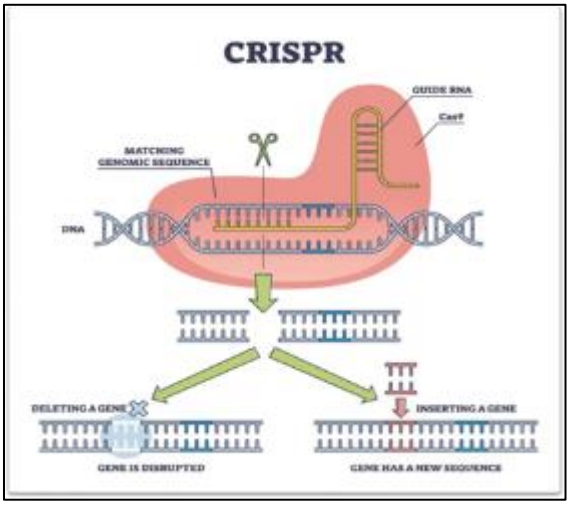

Figure 3 CRISPR-Cas9 Gene Editing: Guide RNA directs the Cas9 enzyme to a matching DNA sequence, where it cuts the DNA. The break can be repaired by deleting a gene (disrupting its function) or inserting a new gene (introducing a new sequence)

Table 1 History of CRISPR

Year	Milestone	Key Contribution
1987	First Discovery	Ishino et al. found unusual repeat–spacer DNA in E. coli.
2002	Naming CRISPR	Ruud Jansen coined "CRISPR" and identified Cas genes.
2005	Link to Viral Defense	Spacer sequences matched viral DNA → immune role proposed.
2007	Mechanism Proof	Danisco team showed CRISPR provides adaptive immunity.
2012	Gene-Editing Tool	Doudna & Charpentier reprogrammed CRISPR-Cas9.
2013	Human Cell Editing	First successful editing in mammalian cells.
2020	Nobel Prize	Awarded to Doudna & Charpentier for CRISPR-Cas9.
Today	Modern Uses	Medicine, agriculture, environment, advanced CRISPR systems.

3.1. Natural Process of CRISPR

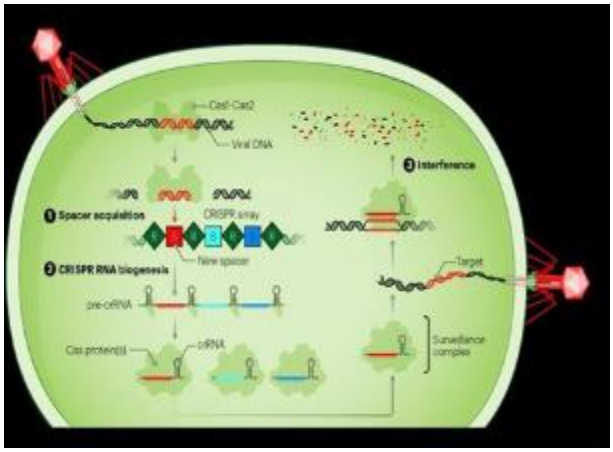

Figure 4 Natural CRISPR–Cas defense mechanism showing virus attack, spacer acquisition, crRNA production, Cas protein activation, and DNA cutting to protect bacteria

3.2. Mechanism of CRISPR Function

CRISPR technology works like a targeted search-and-action tool for genetic material. It is inspired by a natural defense system found in bacteria and other microorganisms, where it is used to recognize and neutralize invading viruses. Scientists have adapted this system for gene editing and epigenetic editing, allowing us to make extremely precise changes to how genes behave.

The core concept is simple: Use a programmable guide (RNA) to direct a specialized protein (Cas) to a specific DNA sequence, where the protein either cuts the DNA or changes its activity.

Step-by-step mechanism

- Designing the Guide RNA (gRNA)
- Formation of the CRISPR–Cas Complex
- Locating the Target DNA
- Action at the Target Site
- The Outcome

3.3. Applications of CRISPR Technology

3.3.1. Medicine and Health

The medical field is one of the main areas where CRISPR is expected to have a major impact. Because it can target very specific DNA sequences, CRISPR can be used to treat genetic disorders at their root cause by correcting or replacing the faulty gene.

Treatment of Genetic Blood Disorders- A breakthrough application is in the treatment of sickle cell disease and β-thalassemia. Both conditions are caused by defects in the hemoglobin gene. In recent clinical trials, scientists collected stem cells from patients, used CRISPR to repair the gene responsible for making hemoglobin, and then returned these edited cells to the patients. The result was life- changing — many patients no longer experienced the painful symptoms of sickle cell disease and became free from regular blood transfusions.

Cell Therapy for Diabetes- CRISPR has also been used experimentally to help people with type 1 diabetes. In one reported case, pancreatic cells were edited so they could produce insulin and resist attacks from the immune system. After these cells were transplanted into the patient, the body began producing its own insulin again something that was not possible before.

Fighting Infections- Scientists are testing CRISPR-based antiviral treatments that can cut up viral DNA or RNA inside infected cells. This approach is being explored for viruses like HIV, hepatitis B, and even certain coronaviruses.

CRISPR is also an essential research tool. It allows scientists to turn genes on or off to study what they do, which helps in understanding how diseases develop.

Disease Models- CRISPR can create precise models of human diseases in animals, making it easier to test potential treatments before trying them in humans.

Gene Function Studies- Researchers can study the role of specific genes in development, behavior, and disease, providing valuable knowledge for future discoveries.

3.4. Limitations of CRISPR Technology

While CRISPR has transformed genetic research, it is not perfect. Like all scientific tools, it has limitations and risks that must be addressed before it can be safely and widely applied, especially in humans. Understanding these limitations is important for making responsible decisions about its use.

3.5. Ethical Issues in CRISPR Use

CRISPR technology is not just a scientific breakthrough — it also raises deep ethical questions about how, when, and why it should be used. Because it allows precise changes to DNA, including in human embryos, CRISPR has the power to permanently alter life in ways never before possible. While this can be used for curing diseases, it can also lead to moral and social dilemmas that society must address.

3.6. Future of CRISPR in Medicine

CRISPR technology is still in its early stages, yet its future in medicine looks extremely promising. Over the next few decades, CRISPR could shift from being a laboratory tool to a mainstream clinical treatment, transforming how we prevent, diagnose, and cure diseases. The combination of precision, affordability, and flexibility means that CRISPR could address medical challenges once considered impossible.

CRISPR Importance:

- High Accuracy and Speed
- Revolution in Medical Treatments
- Impact Beyond Human Medicine
- Epigenetic Editing and Safety
- Boosting Cancer and Brain Research
- Real-Life Breakthroughs
- Scientific World is Excited

4. CRISPR-Based Epigenetic Editing: Mechanism of Action

CRISPR-based epigenetic editing works by changing how genes are expressed without cutting or altering the actual DNA sequence. Instead of removing or replacing genes, this approach uses modified versions of CRISPR tools to turn genes on or off.

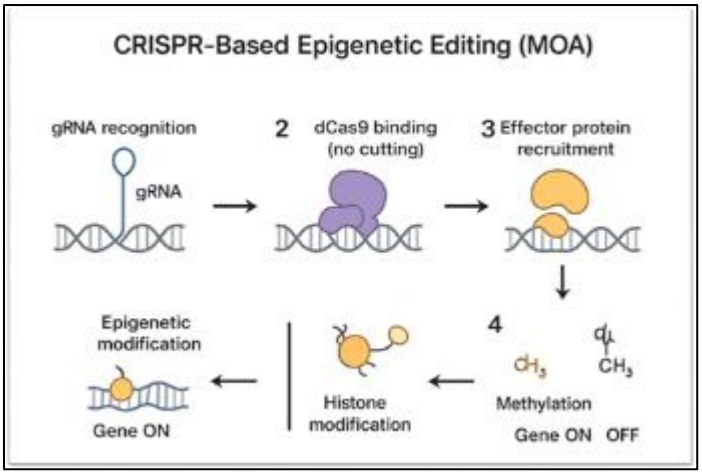

Figure 5 Mechanism of CRISPR-based epigenetic editing. A guide RNA (gRNA) directs dCas9 to the target DNA without cutting, where effector proteins introduce epigenetic modifications (e.g., histone acetylation or DNA methylation), resulting in activation or repression of gene expression without altering the DNA sequence

Table 2 Application Of CRISPR – Based Epigenetic Editing

Application Area	Description	Example/Outcome
Disease Treatment without DNA Modification	Adjusts abnormal gene expression without changing DNA sequence.	Silencing cancer genes, reactivating protective genes.
Cancer Therapy	Switches off oncogenes or activates tumor suppressor genes.	Targeted alternative to chemotherapy.
Neurological & Psychiatric Disorders	Restores normal gene activity in neurons.	Alzheimer's, Parkinson's, depression, autism.
Cardiovascular Diseases	Regulates genes for blood pressure, cholesterol, inflammation.	Potential therapies for heart disease and stroke.
Diabetes & Metabolic Disorders	Modifies gene expression in insulin and fat metabolism pathways.	Diabetes and obesity treatment.
Immune System Regulation	Fine-tunes immune activity by silencing or activating immune genes.	Lupus, rheumatoid arthritis, autoimmune disorders.
Infectious Diseases	Blocks or erases virus- induced epigenetic changes.	HIV, hepatitis, COVID-19.
Regenerative Medicine	Reprograms cells for tissue regeneration.	Stem-cell–like reprogramming for organ repair.
Research Tool	Used to study gene regulation and disease mechanisms.	Functional genomics, drug discovery.
Agriculture & Biotechnology	Regulates crop/livestock traits without changing DNA sequence.	Stress-resistant crops, disease-resistant livestock.

4.1. Advantages of CRISPR-Based Epigenetic Editing

CRISPR-based epigenetic editing provides several advantages over traditional gene-editing methods such as CRISPR-Cas9 gene modification. The key benefit is that it changes gene activity without altering the DNA code itself, making it a safer and more flexible approach.

- No Permanent DNA Changes
- Precision Control of Gene Expression

- Reduced Risk of Off-Target Mutations
- Reversibility
- Wide Range of Applications
- Non-Invasive Therapeutic Potential
- Valuable Research Tool
- Ethical Advantage Over Gene Modification
- Potential for Combination Therapies

4.2. Limitations of CRISPR-Based Epigenetic Editing

While CRISPR-based epigenetic editing holds huge promise, it still faces certain scientific, technical, and practical challenges that limit its immediate application in medicine.

- Delivery Challenges
- Temporary Effects
- Incomplete Editing
- Limited Understanding of the Epigenome
- Off-Target Epigenetic Effects
- Difficulty in Measuring Success
- Lack of Long-Term Studies
- Cost and Accessibility
- Ethical and Regulatory Uncertainty

4.3. Ethical Issues In CRISPR-Based Epigenetic Editing

Although epigenetic editing does not permanently alter DNA sequences, it still raises several ethical, social, and regulatory concerns. These issues must be carefully addressed before the technology is widely used in medicine.

- Human Safety and Unintended Effects
- Reversibility vs. Responsibility
- Germline vs. Somatic Editing
- Inequality and Accessibility
- Risk of Misuse
- Informed Consent
- Regulation and Oversight

4.4. Uses

CRISPR-based epigenetic editing is emerging as one of the most powerful tools in modern biotechnology. Unlike traditional CRISPR-Cas9 methods that make permanent DNA cuts, this technique uses deactivated Cas9 (dCas9) fused with epigenetic modifiers to switch genes ON or OFF without altering the underlying genetic code.

Its versatility makes it applicable across a broad range of fields:

- Medical Research & Therapy
- Neuroscience Applications
- Cancer Research
- Regenerative Medicine
- Agriculture & Crop Science
- Industrial Biotechnology
- Environmental Applications

4.5. A New Era of Medicine

It's called a new era of medicine because CRISPR-based epigenetic editing changes how we think about treating diseases — instead of permanently altering the DNA sequence (gene editing), it allows scientists to switch genes on or off, or fine-tune their activity, without cutting or replacing the DNA itself.

Here's why it's considered a breakthrough:

- Precision without permanent damage

Traditional CRISPR-Cas9 cuts DNA, which can cause permanent and sometimes unpredictable changes. CRISPR-based epigenetic editing uses dead Cas9 (dCas9) fused to epigenetic modifiers (e.g., DNA methyltransferases, acetyltransferases) to modify gene expression without changing the DNA letters.This means the effect can be reversible, reducing long-term risks.

- Control over complex diseases

Many chronic and genetic diseases (e.g., cancer, neurological disorders, metabolic syndromes) involve faulty gene regulation, not just faulty gene code. Epigenetic editing targets how genes are read, offering a new way to correct disease pathways.

- Safer, more ethical applications

Because the DNA sequence remains intact, it avoids some ethical concerns linked to permanent germline editing. Potential for safer use in humans — especially in diseases where temporary or tissue- specific changes are enough.

- Wide range of applications
  - Cancer therapy: Reactivating tumor-suppressor genes or silencing oncogenes.
  - Neurological diseases: Adjusting gene activity in neurons without altering DNA.
  - Regenerative medicine: Controlling stem cell differentiation.
  - Precision agriculture: Improving crop traits without creating GMOs in the legal sense.
  - Opens door for reversible medicine
  - Future drugs may use CRISPR-based epigenetic tools as programmable, targeted “gene switches” that can be turned on and off with precision.

5. Conclusion

CRISPR-based epigenetic editing has emerged as one of the most promising innovations in modern biomedical science. Unlike traditional genetic engineering, which alters the actual DNA sequence, this technology works by modifying the epigenetic markers that regulate gene expression. In simpler terms, instead of rewriting the genetic code itself, epigenetic editing changes the “instructions” that decide whether a gene should be turned on or off. This makes the technology reversible, dynamic, and potentially safer, since the DNA sequence remains untouched.

The Importance of this distinction cannot be overstated. One of the major risks of classical gene editing is that any change made to DNA is permanent, and errors (such as off-target mutations) may be passed on to future generations. Epigenetic editing offers an alternative by controlling the outcome of genes without permanently altering them. This flexibility has opened a new era of medicine, where diseases can be managed by regulating gene activity rather than permanently rewriting the genome.

Over the course of this project, we have examined multiple aspects of CRISPR-based epigenetic editing, including its background, mechanism, uses, advantages, and limitations. It is evident that this technology holds remarkable potential in a wide range of fields. In medicine, it could provide solutions for diseases that were once thought untreatable. For example, in cancer, certain genes become abnormally activated or silenced; CRISPR-based epigenetic tools can restore balance by switching them back to their normal state. Similarly, in neurological disorders such as Alzheimer’s or Parkinson’s disease, scientists are exploring how epigenetic editing can protect neurons or enhance memory-related genes. Beyond human medicine, this approach is also being tested in agriculture and biotechnology to improve crop resilience and livestock health, though the focus of this project remains on human disease control.

One of the strongest advantages of epigenetic editing is that it supports personalized medicine. Every individual has a unique genetic and epigenetic profile, which explains why people respond differently to the same disease or treatment. By mapping a patient’s epigenome, doctors may soon be able to design therapies that are custom-made to their needs. Instead of one-size-fits-all treatment, CRISPR-based epigenetic editing could allow precision therapies that are both more effective and less harmful. This represents a paradigm shift in healthcare, moving from generic drugs toward highly specific and individualized treatment strategies. At the same time, we must acknowledge the challenges and limitations that still exist. Delivering CRISPR-based tools into human cells safely and efficiently remains one of the biggest technical barriers. Off-target effects, where unintended genes are modified, could still pose risks even though

epigenetic changes are reversible. Additionally, long- term safety studies are essential to ensure that artificial changes to gene expression do not cause unpredictable side effects. The ethical dimension is equally important. While epigenetic editing may avoid some of the controversies of permanent genetic engineering, questions about misuse, equity of access, and potential long-term consequences remain unresolved. These issues highlight the need for strong international guidelines and careful clinical testing.

Despite these challenges, the future of CRISPR-based epigenetic editing looks extremely promising. Many scientists believe it may eventually become a standard tool in medicine, much like antibiotics or vaccines. In the coming years, we may see its application not only in curing inherited diseases but also in preventing conditions before they occur. For instance, individuals with a family history of cancer or heart disease may undergo preventive epigenetic therapies to reduce their risk. Combined with artificial intelligence and advanced diagnostics, CRISPR-based epigenetic editing could revolutionize healthcare into a predictive and preventive system, rather than one that only reacts after disease develops.

In conclusion, CRISPR-based epigenetic editing represents a true new era of medicine. By bridging the precision of CRISPR with the flexibility of epigenetics, it provides an innovative approach to disease control without gene modification. It offers hope for millions of patients suffering from conditions that currently lack effective treatments. More importantly, it points toward a future where medicine becomes safer, more precise, and deeply personalized. However, as with all powerful technologies, success will depend on balancing innovation with responsibility, ensuring that its use remains ethical, safe, and accessible. If these challenges are carefully addressed, CRISPR-based epigenetic editing could stand alongside the greatest breakthroughs in medical history and redefine how humanity approaches health and disease.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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