Computational Biology Approach: A Journey from Gene Editing to Adult's Mental Health

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Abstract

This research explores the intricate relationship between gene editing, DNA transcription, translocation mechanisms, and their impact on the mental health of individuals aged 18 and above. It seeks to contribute novel insights to this underexplored intersection, propose potential therapeutic interventions, and offer avenues for further exploration. The study extensively reviews two prominent gene-editing technologies: CRISPR-Cas9 and TALENs. It elucidates their mechanisms and identifies potential errors occurring during the final stages of Non-Homologous End Joining (NHEJ), which may lead to gene disruptions and mutations. These disruptions can significantly affect crucial gene functions related to neural regulation, brain development, and mental health disorders. Moreover, the study emphasizes the significance of Homology-Directed Repair (HDR) and its precision in effecting precise DNA sequence changes. It highlights the potential for errors during this process and their direct implications for neural processes and mental health. To address the impact of gene editing on mental health, a computational methodology using Python and the Biopython library is proposed. Focusing on the CRISPR-Cas9 method's activity on the IDH1 gene, which is associated with brain cancer, real-time monitoring through Bioluminescence Imaging (BLI) is recommended as a valuable tool for assessing gene editing efficiency and specific

I. Introduction

i. Genetic Editing and Its Relevance:

As the world trends towards gene editing, it's crucial to carefully consider its impact—not just the immediate benefits, but also the potential unintended consequences that can arise when venturing into uncharted territories without fully exploring the side effects. Gene editing, a form of genetic engineering, encompasses the addition, removal, alteration, or substitution of DNA within the genome of a living organism. Unlike earlier genetic engineering techniques that haphazardly integrated genetic material into a host genome, genome editing is precise, targeting specific sites for insertions.[1].

The process involves recognizing target genomic locations and the binding of effector DNA-binding domains (DBDs), leading to the creation of double-strand breaks (DSBs) in the target DNA via restriction endonucleases (FokI and Cas). These DSBs are then repaired through homology-directed recombination (HDR) or non-homologous end joining (NHEJ),

constituting the fundamental mechanisms underlying genetic manipulations through programmable nucleases [2].

Future trends toward gene editing as it has a bright future because of many factors like easily available tools, technological advancements, increased funding, and the potential for individualized treatments [3]. Another crucial factor is the intersection of computation and biology. To analyze complex genetic data and simulate the effects of gene editing, computational tools are becoming increasingly important. The precision and effectiveness of gene editing are improved by this convergence. Gene editing is now a crucial part of state-of-the-art therapeutic strategies for a range of genetic diseases and conditions as a result of the convergence of scientific and technological advancements.

Unfortunately, gene editing is a double-edged weapon. As many as its advantages, it has many disadvantages. The disadvantages of gene editing are explored in [4]. particularly in light of the ethical and societal concerns raised by recent events. One such example is the case of gene editing in Chinese twins [5], which drew attention to the ethical dilemmas surrounding germline editing. Germline editing involves modifying the genetic makeup of embryos, which raises ethical concerns about the unintended consequences of altering future generations' DNA. This approach can lead to unintended genetic mutations and unpredictable long-term effects, emphasizing the risks associated with altering the human genome. Moreover, the potential for gene editing to be used for enhancement purposes rather than therapeutic reasons raises ethical questions about creating a "designer baby", where genetic traits are selected and manipulated for non-medical purposes.

ii. DNA Transcription and Transposition:

In an ocean full of complex processes, DNA transcription, and transportation mechanisms arise as the most important processes that affect everything in the human body [6]. DNA transposition refers to the process by which segments of DNA are relocated from one genomic location to another [7]. DNA transposition plays a crucial role in shaping genetic diversity within populations. Transposable elements can transport genetic information as they move from one genomic location to another. This movement may introduce fresh genetic variations, which will increase population diversity. These transposable elements might have regulatory components, functional genes, or sequences that have the power to affect traits and phenotypes [8].

The most important Genetic process is DNA transcription. A DNA segment is copied into RNA during transcription. Messenger RNA (mRNA) is the term for DNA segments that are transcribed into RNA molecules that can encode proteins. Non-coding RNAs (ncRNAs) are RNA molecules that contain copies of additional DNA segments [9]. As the importance of this, any error can result in a huge disaster in the human body. Errors in DNA transcription, as discussed by [10] can pose significant dangers to cellular function and genetic integrity. When the transcription process is prematurely cut off due to errors, it results in incomplete or aberrant messenger RNA (mRNA) molecules. These faulty mRNAs can lead to the production of non-functional or malfunctioning proteins, disrupting normal cellular processes. Additionally, defective mRNA can trigger cellular stress responses and activate mechanisms like nonsense-mediated mRNA decay [11]which prevents the translation of flawed mRNAs. Such errors in transcription

can contribute to genetic disorders, cellular dysfunction, and disease by compromising the accurate translation of genetic information into functional proteins.

iii. Nexus Between Mental Health and DNA Processes:

Mental health problems have become significant in the biological world. A study in the USA estimated that around 18 to 26 percent of Americans aged 18 and older—about 1 in 5 adults—suffer from a diagnosable mental disorder [12]. The well-being of a sizeable portion of the adult population is put at risk by this sizeable number. Genetics is the primary cause of mental health disorders. Susceptibility to mental health disorders like depression, anxiety, schizophrenia, and bipolar disorder is significantly influenced by genetic factors. Genetic variations in key neural processes, including neural development and neurotransmitter regulation, influence an individual's vulnerability. These genetic factors interact with environmental stressors [13]as explained by the diathesis-stress model, where individuals with genetic predispositions are more prone to disorders when exposed to stress. Genetic explanations can reduce stigma by highlighting the biological nature of these conditions [14].

The most significant impact on mental health problems is a result of DNA transposition. Transportation is the movement of genetic material within a person's DNA. This movement may exacerbate mental disorders if it interferes with genes involved in neurotransmitter regulation, neural development, or other aspects of mental health [15]. Gene disruption may result in altered brain physiology or structure, affecting mood, cognition, and behavior. Furthermore, transpositional events close to regulatory regions may alter gene expression profiles, resulting in imbalances in neurotransmitters or other signaling molecules that are essential for preserving mental health. Such interruptions may raise the possibility of mental health disorders.

Although Transcription is crucial for normal cellular function, disruptions in transcriptional regulation can play a significant role in mental health disorders. Stress-related psychiatric disorders such as depression, anxiety, and post-traumatic stress disorder (PTSD) often involve altered gene expression patterns. Epigenetic modifications, chemical changes to DNA, and associated proteins can influence transcription [16]. Stressful experiences can lead to epigenetic changes that affect gene expression in response to environmental factors [17] These modifications, such as DNA methylation and histone modifications, can silence or activate specific genes involved in stress response and neural function.

iv. The Objectives:

Our scholarly research aims to elucidate the question: "How can computational biology be leveraged to unravel the DNA transcription and transposition mechanisms resulting from gene editing that impact the mental health of individuals above 18?" By collecting data, we will emphasize the relationship between gene editing, and its impacts on DNA transposition and translocation, and Mental health disorders.

After analyzing data, we aim to utilize computational biology to harness all its benefits in modeling and detecting the processes of the effects of genetic editing on DNA transcription and translocation, which have a negative impact on mental health in order to propose potential therapeutic interventions for a cure.

II. Literature review

This section aims to provide a comprehensive overview of the literature relevant to this research paper. It will summarize the potential mental issues that arise from the negative effect of gene editing, by monitoring DNA transposition and transcription between them. Each paragraph in **subsection-i** and **subsection-ii** will reference a specific paper and present a concise summary of its findings. Additionally, **subsection iii** will highlight the unique contributions of our work.

To conduct the literature search, Google Scholar was employed as the search engine. The keywords "gene editing," "Mental health issues," "DNA transcription disruption " and "DNA transposition" were utilized to retrieve relevant publications. The identified papers were then categorized based on their relevance, with the least relevant paper listed first and the most relevant paper listed last.

ii. Uncontrolled Gene Editing: Implications and Risks:

In [18], the CRISPR/Cas system and its synergy with open-access genetic data have driven a surge in genome editing research for cereal crop enhancement, such as maize, wheat, barley, and others. Editing outcomes, categorized as SDN-1, SDN-2, and SDN-3, rely on DSB repair mechanisms. Genome editing methods, including CRISPR/Cas9, Zinc finger nucleases, TALENs, and base editing, have been applied in cereals. In the first generation, there is an improvement in cereal crops. However, in further generations, researchers have realized that many negative mutations have occurred in cereal crops.

The paper [19] demonstrates that Gene editing techniques like ZFPs and TALEs show promise for mitochondrial DNA (mtDNA) editing. However, they face limitations in delivery efficiency and cost-intensive production. CRISPR/Cas9, with its simplicity, could revolutionize mtDNA editing, but effective delivery of exogenous sgRNA into mitochondria remains a challenge. Recent studies suggest using stem-loop motifs and mitochondrial targeting sequences (MTSs) to deliver sgRNA, providing a proof of concept for this approach. Engineered Cas9 and Cas12a linked with MTSs show potential for efficient delivery. Additionally, virus-like particles (eVLPs) have emerged as a promising transient ribonucleoprotein (RNP) delivery platform for minimal off-target editing. Further optimization is needed for clinical applications of these gene-editing platforms in mtDNA editing.

In [20], it demonstrates that Gene editing in human embryos has raised substantial ethical and practical concerns. While it holds potential for addressing genetic disorders, unintended negative effects have emerged. These include off-target mutations and mosaicism, where only a subset of cells carries the desired genetic alteration. Such genetic variability can result in unpredictable health consequences, underscoring the need for cautious consideration of the benefits and risks associated with human embryo genome editing. Ethical and regulatory frameworks must guide its responsible use to prevent unintended and harmful genetic outcomes.

In [21], The discussed article examines the readiness for genome editing in human embryos for clinical applications. It raises concerns about the potential negative consequences of such genetic interventions. The research highlights the need for careful consideration and ethical scrutiny in utilizing gene editing technologies in human embryos due to the uncertain long-term effects and

ethical dilemmas associated with altering the human germline. The article underscores the importance of comprehensive ethical and scientific evaluation before clinical implementation.

In [22], This study delves into the complex realm of human germline genome editing, highlighting its potentially detrimental consequences. Researchers observed negative outcomes, with unintended mutations occurring in subsequent generations. The occurring mutation can be Theta mutations, which can occur as a result of various genetic processes, including gene editing. Another type of mutation is a point mutation, where a single nucleotide base in the DNA sequence is altered.

In [23], The experiments leading to the first gene-edited babies exposed several negative effects. Firstly, there were unintended genetic mutations and off-target edits, raising concerns about the precision and safety of gene editing techniques. Additionally, ethical failings included a lack of informed consent, transparency, and oversight, which posed significant ethical dilemmas. These issues highlighted the potential for irreversible harm to individuals and future generations, underlining the pressing need for more stringent governance and ethical standards in genetic editing research.

In [24], Genome editing, particularly in human embryos, introduces the potential for negative mutations that can extend to future generations. These unintended genetic alterations may manifest as unexpected health issues, potentially compromising the intended benefits of gene editing. The study underscores the importance of informed consent as a safeguard against these undesirable genetic changes, highlighting the ethical and scientific complexities surrounding gene editing in the context of its potential negative mutation effects.

The study [25], demonstrates that Gene editing has raised ethical concerns due to potential negative effects. Initial improvements in edited crops may be overshadowed by unintended mutations in subsequent generations. Ethical considerations revolve around unintended consequences, such as off-target genetic alterations, which can pose risks to human health and the environment. Striking a balance between technological advancements and ethical responsibility is crucial in the context of gene editing to ensure its safe and responsible application in medicine and agriculture.

The study [26] demonstrates that the p53-mediated DNA damage response, triggered by CRISPR-Cas9 genome editing, significantly impacts DNA transcription. When DNA damage occurs during gene editing, p53 activates various cellular responses, including the transcription of genes involved in DNA repair and cell cycle arrest. This ensures that the cell can mend damaged DNA before progressing through the cell cycle. However, the overactivation or prolonged presence of p53 may lead to detrimental effects. Excessive p53 activation can suppress genes essential for cell survival and growth, disrupting normal DNA transcription and potentially causing cell cycle arrest or cell death. Additionally, DNA repair during gene editing may introduce errors or mutations, further influencing transcription. Thus, precise control and monitoring of CRISPR-Cas9 editing are crucial to minimize unwanted transcriptional alterations.

The study [28], shows that Gene editing can significantly impact DNA transcription. When genetic material is

modified through editing techniques, it may disrupt the normal transcription process. Errors in the editing process, including unintended mutations or gene insertions, can interfere with the binding of transcription factors or RNA polymerases to the target gene, leading to altered or impaired transcription. Furthermore, off-target effects of gene editing can result in unintended changes in nearby genes, potentially affecting their transcription as well. To harness the full potential of gene editing while minimizing these disruptions, precise and controlled editing methods are essential to ensure minimal interference with DNA transcription and gene expression.

Gene editing using viral vectors can have a significant impact on DNA transcription as mentioned in the study [29]. While these vectors are designed to target specific genes and introduce desired changes, unintended mutations, and off-target effects can disrupt normal DNA transcription processes. Such disruptions may lead to the dysregulation of gene expression, potentially resulting in the overexpression or under expression of critical genes. These alterations can have cascading effects on cellular functions, potentially contributing to the development of diseases or other undesirable outcomes. Therefore, understanding and minimizing the impact of gene editing on DNA transcription is crucial for the safe and effective application of this technology in gene therapy and other biomedical fields. Our paper is different from this paper because our paper will model and mentor the process of impact to make it easier to suggest potential core.

In [30], Gene editing techniques, like CRISPR-Cas9, can inadvertently impact DNA translocation, which is the movement of genetic material from one location to another in the genome. This can result in unintended structural changes. The introduction of double-strand breaks (DSBs) by CRISPR-Cas9 can stimulate DNA repair mechanisms. In some cases, non-homologous end joining (NHEJ) may cause imprecise repair, leading to DNA translocations. Additionally, homology-directed repair (HDR) used in gene editing might introduce sequences that differ from the original, influencing translocation events. These alterations may disrupt normal gene function, potentially contributing to genetic instability or diseases. Understanding and mitigating these effects is crucial for safe and effective gene editing applications. Our paper is different from this paper because our paper will model and mentor the process of impact to make it easier to suggest potential core.

ii. The Genetic Contribution to Mental Health Issues:

The study [31] shows that environmental factors significantly impact mental health, playing a pivotal role in shaping one's psychological well-being. Such influences can lead to adverse mental health outcomes, with long-lasting repercussions. These effects underscore the importance of understanding the intricate relationship between the environment and mental health, as they are intertwined in ways that necessitate careful consideration and ongoing research for comprehensive mental health support and interventions.

In the study [32], Genetic factors play a substantial role in the development of mental illnesses, as evidenced by a genome scan on a sizable bipolar pedigree sample. The study identified significant linkage signals on various chromosomes associated with bipolar disorder, psychosis, suicidal behavior, and panic disorder. Notable regions included 10q25, 10p12, 16q24, 16p13, and 16p12 for standard diagnostic models, and 6q25 (suicidal behavior), 7q21 (panic disorder), and 16p12 (psychosis) for

phenotypic subtypes. Many other regions also showed suggestive linkage, underscoring the genetic complexity of mental illness. The findings emphasize the need to dissect disease phenotypes to expedite the search for susceptibility genes.

The study [33] Genetic factors have been implicated in the development of various mental health disorders. Mutations in genes encoding DNA repair enzymes, such as topoisomerase I-dependent DNA damage repair enzyme TDP1, have been associated with conditions like spinocerebellar ataxia with axonal neuropathy. These genetic mutations can disrupt crucial cellular processes, leading to neuronal dysfunction and contributing to the manifestation of mental health issues. Understanding the negative impact of genetic factors on mental health highlights the importance of genetic research and personalized approaches to diagnosis and treatment in psychiatry and neurology.

In the study [34], Genetic factors play a significant role in the development of mental illnesses, contributing to their negative impact. Research in the field has shown that transposable elements and their epigenetic regulation are associated with mental disorders. These genetic elements can disrupt normal brain functions and contribute to the susceptibility of individuals to conditions such as depression, schizophrenia, and bipolar disorder. The intricate interplay between genetic factors and mental illness highlights the complex nature of these conditions, making treatment and management challenging and often less effective.

The paper [35] discusses the impact of DNA translocation and transportation on mental health outcomes in individuals exposed to early-life social adversity. It highlights the role of epigenetic modifications in response to adverse environments, potentially influencing mental health. The study underscores how social adversity can trigger changes in DNA regulation, leading to lasting effects on mental well-being. These findings emphasize the significance of understanding the epigenetic mechanisms involved in mental health vulnerability related to early-life social challenges. Our paper is different from this one, as our focus is on the distribution of DNA translocation and transcription resulting from gene editing.

i. Our Contribution:

Our paper aims to address the existing paucity of literature concerning the deleterious effects of gene editing and its intricate interplay with DNA transposition and transcription, as they relate to mental health outcomes. While considerable research has been conducted on this topic as outlined in **subsections i and ii** our study seeks to make noteworthy contributions in the following ways:

- Concentrating our investigation on a specific demographic: adults aged 18 and above.
- Establishing a comprehensive understanding of the nexus between gene editing and mental health concerns, with a particular focus on the linkage provided by DNA transposition and transcription processes.
- Utilizing computational biology methodologies to model and discern how gene editing processes impact mental health, with the ultimate goal of proposing potential avenues for intervention.

To the best of our knowledge, our contributions are original and introduce novel insights to the existing body of literature. This assertion is substantiated by the thorough review presented in both **subsections i and ii.**

III. Genetic Editing and Mental Health

i. CRISPR-Cas9 System:

CRISPR-Cas9's revolutionary gene-editing technology allows for precise manipulation of DNA. It entails using a single-guide RNA (sgRNA) to direct the Cas9 enzyme to particular DNA sequences. When Cas9 reaches its target, it causes DNA double-strand breaks. The cell's repair system then fixes these breaks, frequently through insertions or deletions (indels), which disrupts the gene. For more specific changes, a repair template can be offered as an alternative. Genes can be silenced, activated, corrected of mutations, and even have reporter genes inserted using this technology. Additionally, it makes it easier to study non-coding RNAs and epigenetic changes. The adaptability of CRISPR-Cas9 revolutionizes genetic research and has enormous therapeutic potential. CRISPR-Cas9's system is **shown in Figure 1** [36]

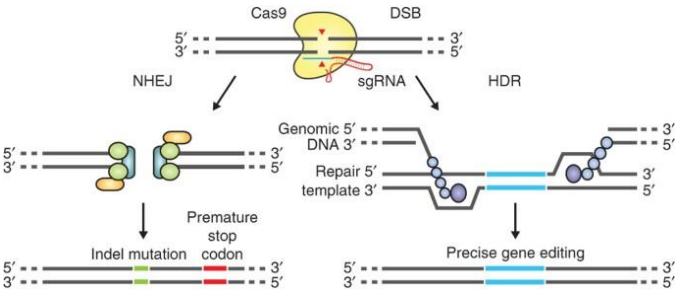

Figure 1 shows the CRISPR-Cas9 system [36]

The CRISPR-Cas9 system affects mental health in many ways, starting with the designing of a Guide RNA (gRNA). In CRISPR-Cas9 gene editing, a specific gRNA is designed to target a particular DNA sequence within the genome. This gRNA serves as a guide for the Cas9 protein to find its target. Once the Cas9 protein is guided to the target DNA sequence by the gRNA, it acts like a pair of 'molecular scissors' and cuts (cas9 cleavage) the DNA at that precise location. This is known as a double-stranded break. After this occurs, it follows two pathways for natural repair as will be discussed in subsection iii

ii. Influence of TALENs on Mental Health:

Transcription Activator-Like Effector Nucleases (TALENs) are a powerful gene-editing technique that has emerged as an improvement over the Zinc Finger Proteins method. **As shown in Figure 2** [39], the creation of TALEN constructs constitutes the initial step in the TALEN gene-editing procedure. Each TALEN comprises a DNA-binding domain derived from TALE proteins and a nuclease domain derived from the FokI endonuclease. Together, these two TALENs target one strand of the DNA double helix at the intended editing site[39].

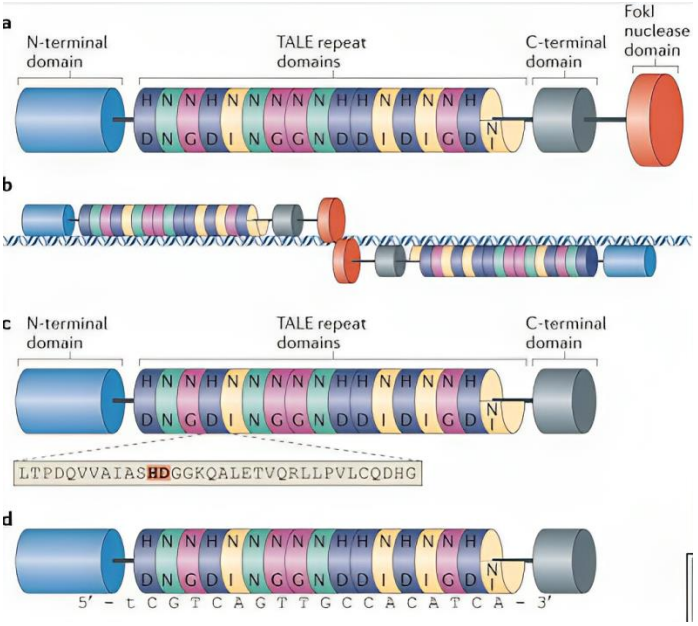

Figure 2 shows TALEN mechanism [39].

- TALEN Structure

TALENs consist of TALE repeats, represented as colored cylinders, and a carboxy-terminal truncated "half" repeat. Each TALE repeat contains two hypervariable residues represented by letters. The TALE-derived amino- and carboxy-terminal domains, essential for DNA binding, are depicted as blue and grey cylinders, respectively. The

non-specific nuclease domain from the FokI endonuclease is illustrated as a larger orange cylinder.

- TALEN Binding and Cleavage

TALENs function as dimers, binding to the target DNA site. The TALE-derived amino- and carboxy-terminal domains flanking the repeats may interact with the DNA. Cleavage by the FokI domains occurs within the "spacer" sequence, located between the two regions of DNA bound by the two TALEN monomers.

- TALE-Derived DNA-Binding Domain:

A schematic diagram illustrates the structure of a TALE-derived DNA-binding domain. The amino acid sequence of a single TALE repeat is expanded below, with the two hypervariable residues highlighted in orange and bold text.

- TALE-Derived DNA-Binding Domain Aligned with Target DNA

The TALE-derived DNA-binding domain is aligned with its target DNA sequence. The alignment shows how the repeat domains of TALEs correspond to single bases in the target DNA site according to the TALE code. A 5' thymine preceding the first base bound by a TALE repeat is indicated

iii.The Errors Have Invaded Everything:

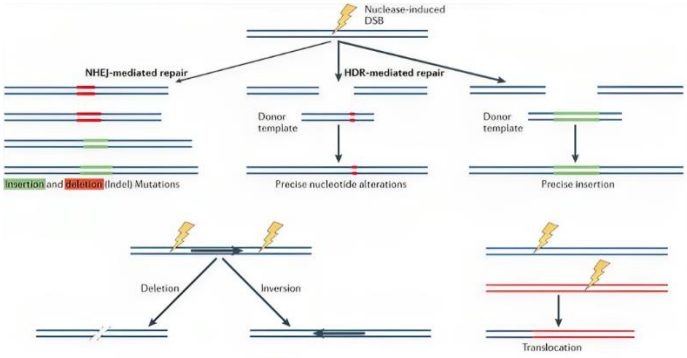

Figure 3 show the DNA repairing mechanism pathways [39]

After the gene editing occurred however the process followed it goes for two pathways to repaired **as shown in figure 3**:

First pathway is Non-Homologous End Joining (NHEJ): This pathway, occurring without template, attempts to directly join the broken ends of the DNA. Always it goes to this pathway. It can introduce small insertions or deletions (indels) in the process, often resulting in gene disruptions. As shown in Figure 2, NHEJ begins with the binding of the Ku80-Ku70 heterodimer to the broken DNA ends. This complex then recruits DNA-PKcs. Notably, DNA-PK is not present in yeast. Several proteins, including Artemis, polynucleotide kinase (PNK), and members of the polymerase X family, process the DNA ends in preparation for the next steps. In the final step, ligase IV, working in conjunction with its co-factors Xrcc4 and Cernunos/Xlf, joins the DNA ends together [37]

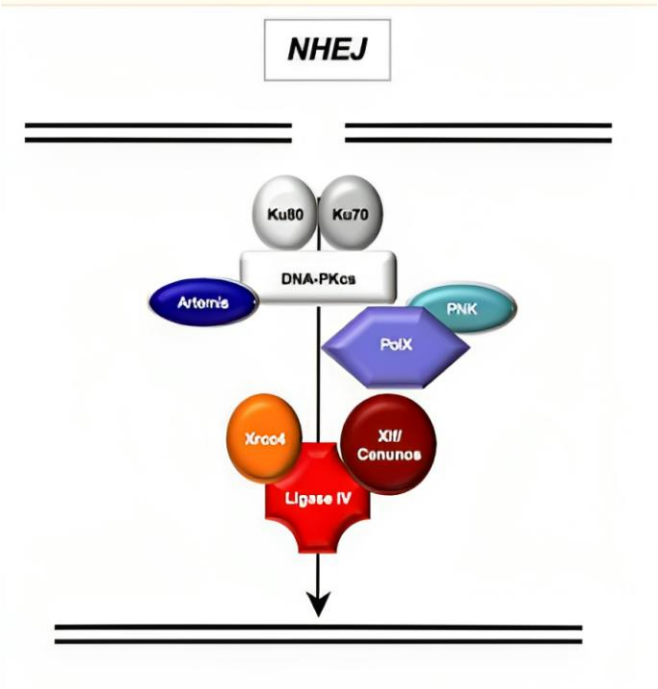

Figure 4 shows the NHEJ pathway [37]

The error in the non-homologous end joining (NHEJ) typically happens when the DNA's broken ends are region. Because NHEJ does not rely on a template to direct the repair process, it is an error-prone repair mechanism. Instead, the two ends of the broken DNA strands are directly joined or ligated [37]. In some case the survivable gene can be only 0.1% as the DNA cleavages again [38].

Because there is no template and the NHEJ process is fast, small insertions or deletions (indels) can occur at the repair site. These indels have the potential to cause mutations, gene disruptions, or frame-shift mutations, all of which could have an impact on how well the gene and the protein it encodes function. As a result, the error-prone nature of NHEJ is primarily associated with the rejoining step, where errors can occur.

Many genes that are disrupted can have repercussions for neural function, brain development, and mental health conditions. However, this can occur due to decreased or altered key gene responses for neurotransmitter regulation. This, in turn, can cause transcription deficiencies or translocation of DNA sequences. For instance, error-prone NGEJ can lead to deficiencies in the DLG3 (Discs, large homolog 3) gene, which is responsible for memory and learning. Mutations in this gene can result in Intellectual Disability, Speech and Language Delays, and other neural disorders.

The second pathway is Homology-Directed Repair (HDR): In this pathway, a template DNA molecule is used to repair the break, allowing for precise DNA sequence changes to be introduced during repair. These repairs occurred by ordered steps **as shown is Figure 5:**

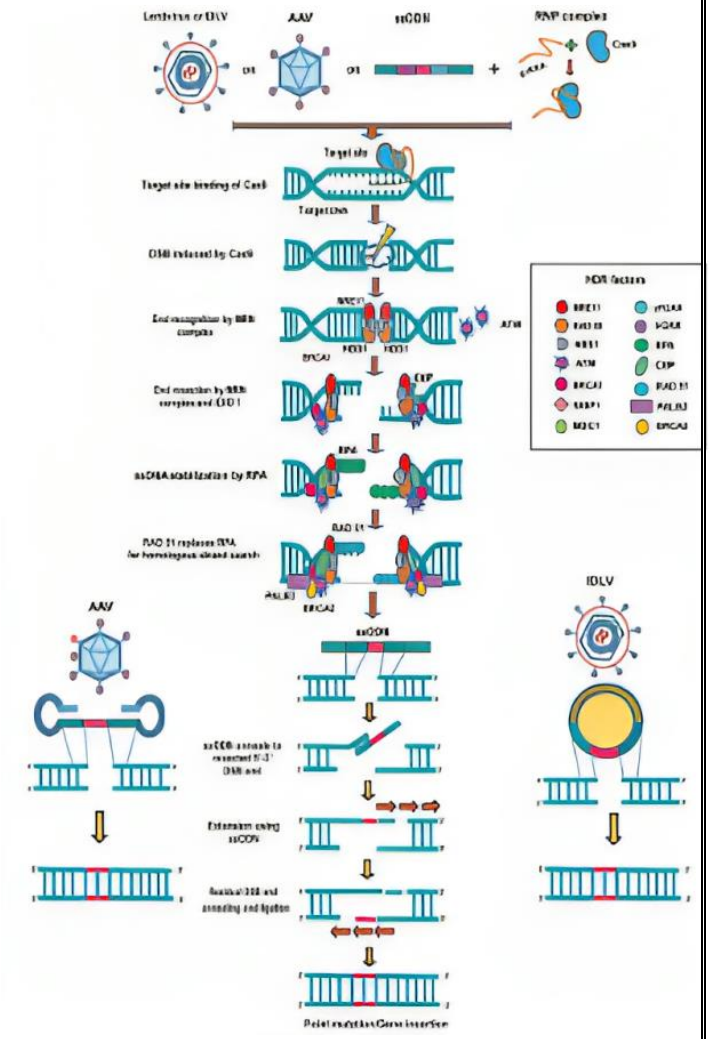

Figure 5 show HDR pathway [40]

In the intricate process of HDR (Homology-Directed Repair) following gene editing, a highly coordinated sequence of events unfolds to facilitate the precise and faithful repair of double-strand breaks (DSBs) in the DNA. Initially, the occurrence of DSBs activates the ATM checkpoint, a critical regulator of DNA repair processes and cell cycle progression. This activation is a crucial trigger for subsequent repair steps. During the S-phase of the cell cycle, CDK-mediated phosphorylation of CtIP at S372 plays a pivotal role in priming CtIP for action, ultimately leading to the formation of the BRCA1-CtIP complex. This complex is responsible for modifying

the chromatin environment around the DSB site, making it conducive to DNA end resection.

The MRN complex (comprising MRE11, RAD50, and NBS1 proteins) forms a major complex with BRCA1-CtIP, and it contributes significantly to the repair process by generating a short 3' overhanging single-stranded DNA via the nuclease activity of MRE11. This newly generated single-stranded DNA is immediately stabilized by replication protein A (RPA), preventing its degradation or unintended interactions. Continuing the repair process, the short single-stranded DNA undergoes further extension through the action of a complex that involves helicases and nucleases like BLM, EXO1, WRN, and DNA2. Simultaneously, the activation of the ATR cell cycle checkpoint adds an additional layer of control to the process.

With the single-stranded DNA prepared and stabilized, the pivotal step of RAD51 loading ensues. RAD51 displaces RPA from the single-stranded DNA and forms nucleoprotein filaments, setting the stage for homologous search and invasion of the repair template. It's important to note that the specific mechanisms involved may vary depending on the type of HDR being employed, which can include canonical HDR, synthesis-dependent strand annealing (SDSA), break-induced replication (BIR), single-stranded annealing (SSA), or single-stranded templated repair (SSTR) [40].

However, HDR is an accurate process that utilizes a template and operates at a slower pace compared to the more rapid NHEJ pathway. Nonetheless, HDR is less efficient than NHEJ, especially that it occurs only during the S and G2 phases of the cell cycle when sister chromatids are available as repair templates. If gene editing occurs during other phases of the cell cycle, NHEJ may be favored, potentially leading to errors. Furthermore, even when a repair template is provided, the cell may still prefer the NHEJ pathway, resulting in the generation of small insertions or deletions (indels) rather than precise edits.

Errors can also arise if the provided repair template does not perfectly match the target DNA sequence or if there are mismatches or mutations within the repair template itself. These discrepancies can lead to inaccurate editing outcomes. Additionally, the HDR process may occasionally fail to complete as expected, leaving the DNA with a partial modification or an incomplete integration of the repair template.

In the context of genes related to mental health, any disruption in the cell cycle, such as halting at the G2 phase due to the inability to produce spindle fibers, can have direct effects. Errors in HDR, especially when targeting genes associated with mental health, may result in functional alterations that can impact neural processes.

IV. Computational methodology

As our research objective trends toward collecting data and concluding the process by which gene editing affects mental health, in this section, we will model this process using figures, which will be demonstrated in the discussion section. Our model will rely on the Python language with the Biopython library. We chose this library because it is a flexible and user-friendly Python library for modeling biological processes. It offers a wide range of features, compatibility across platforms, interoperability with bioinformatics tools, and strong community support. It is an important tool for computational biology research due to its open-source nature, scalability, and integration with data analysis libraries.

In this modeling, we utilized the CRISPR method, one of the most commonly used gene editing methods recently, and the IDH1 gene with its sequence 'ACGTGCAGCTGGGTGGTTGTGGTTTGCTTGGCT TGAGAAGCAGGTTA.....', as it is the gene responsible for 50% of gliomas (brain cancer). Mutations in this gene, after NHEJ occurs, can lead to not only a lack of cancer cure but also abnormal production of 2-hydroxyglutarate (2-HG), an oncometabolite. This metabolic change interferes with numerous cellular pathways, primarily in the cytoplasm, affecting epigenetic control and causing DNA hypermethylation. These metabolic changes primarily drive cancer progression but can also indirectly impact mental health. Abnormal metabolites and related disruptions may induce neuroinflammation, neurotransmitter imbalances, and other neurological effects, potentially affecting mood and cognitive abilities [40].

The model description is demonstrated in **subsection i**, and code for simulation are demonstrated in **subsection ii**, where the code description will display the code.

i. Code Description:

1. Importing Libraries:

```
from Bio.Seq import Seq
from Bio.SeqUtils import MeltingTemp
from Bio.Restriction import BsmBI
```

Description:

- **Bio.Seq** and **Bio.SeqUtils** are modules from the BioPython library used for manipulating DNA sequences and calculating properties such as melting temperature (Tm).
- **Bio.Restriction** is another module from BioPython that is utilized to simulate the recognition site of the Cas9 protein.

2.Defining Protein and DNA Classes

```
class Protein:
    def __init__(self, name):
        self.name = name
        self.phosphorylated = False

class DNA:
    def __init__(self, sequence):
        self.sequence = sequence
```

Description:

In this section, we define Python classes to represent biological entities. Protein objects have attributes such as name and phosphorylated to model the phosphorylation status. DNA objects encapsulate DNA sequences.

3. Defining Protein and DNA Entities:

```
ATM = Protein("ATM")
CDK = Protein("CDK")
CtIP = Protein("CtIP")
BRCA1 = Protein("BRCA1")
Ku80_Ku70 = Protein("Ku80-Ku70")
DNA_PKcs = Protein("DNA-PKcs")
Artemis = Protein("Artemis")
PNK = Protein("Polynucleotide Kinase (PNK)")
DNA_polymerase_X = Protein("DNA Polymerase X")
ligase_IV = Protein("Ligase IV")
Xrcc4 = Protein("Xrcc4")
Cernunos_Xlf = Protein("Cernunos/Xlf")

target_sequence = "ACGTGCAGCTGGGTGGTTGTGGTTTGCTTGGCTTGAGAAGCAGGTTAAGCTGGTG
dsb_site = DNA(target_sequence)
```

Description:

We instantiate specific biological entities using the defined classes. For example, **ATM**, **CDK**, **CtIP**, and **BRCA1** represent proteins, while **dsb_site** represents a DNA sequence. These entities model key molecules and the DNA site of gene editing. Each protein has a name and a **phosphorylated** attribute, which can be set to **True** or **False** to simulate phosphorylation status. DNA sequences are represented as strings in the **DNA** class.

4. Designing gRNA:

```
def design_gRNA(target_sequence):
    # ... (Code for designing gRNA)
```

Description:

The **design_gRNA** function is used to design a guide RNA (gRNA) for the target DNA sequence. The gRNA is designed based on specific criteria, including melting temperature and the absence of Cas9 recognition sites.

5. Designing Conditions X and Y:

```
condition_X = bool(repair_template)
condition_Y = not condition_X
```

Description:

Two conditions, X and Y, are defined based on the presence or absence of a suitable repair template.

condition_X is **True** if a gRNA is designed, indicating the activation of the Homology-Directed Repair (HDR) pathway.

condition_Y is the inverse of **condition_X**, representing the activation of the Non-Homologous End Joining (NHEJ) pathway if no repair template found.

6. Simulation of HDR Pathway:

```
def perform_HDR():
    # ... (Simulation of HDR pathway)
```

Description:

The **perform_HDR** function simulates the sequential steps of the Homology-Directed Repair (HDR) pathway following gene editing. It includes events such as the activation of the ATM checkpoint, phosphorylation events, formation of protein complexes, and additional HDR-specific interactions.

7. Simulation of NHEJ Pathway:

```
def perform_NHEJ():
    # ... (Simulation of NHEJ pathway)
```

Description:

The **perform_NHEJ** function simulates the stages of the Non-Homologous End Joining (NHEJ) pathway following gene editing. It encompasses events such as the binding of the Ku80-Ku70 heterodimer, recruitment of DNA-PKcs, DNA end processing, and DNA end ligation.

8. Mutation in IDH1 Gene:

```
IDH1_mutated = True
```

Description:

Within the NHEJ pathway simulation, we introduce a step to simulate mutations in the IDH1 gene caused by NHEJ. IDH1_mutated is set to True to indicate the occurrence of mutations.

9. Effects of IDH1 Mutations on Cellular Processes:

```
if IDH1_mutated:
    # ... (Description of effects)
```

Description:

Following the simulation of IDH1 mutations, we provide a descriptive account of the effects of these mutations on cellular processes.

This includes the production of abnormal isocitrate dehydrogenase (IDH) enzymes, generation of oncometabolite 2-hydroxyglutarate (2-HG), disruption of cellular pathways, competition with isocitrate, loss of function in wild-type IDH enzymes, and disruption of epigenetic regulation.

10. Mental Health Impact:

```
if IDH1_mutated:
    # ... (Description of mental health impact)
```

Description:

We briefly outline the potential effects of the cellular changes resulting from IDH1 mutations on mental health. This encompasses concepts such as abnormal metabolites (e.g., 2-HG), neuroinflammation, neurotransmitter imbalances, neurological effects, mood alterations, and cognitive processes.

ii. The Code:

```
from Bio.Seq import Seq
from Bio.SeqUtils import MeltingTemp
from Bio.Restriction import BsmBI  # Simulate Cas9 recognition site

class Protein:
    def __init__(self, name):
        self.name = name
        self.phosphorylated = False
        # Additional attributes and methods specific to the protein

class DNA:
    def __init__(self, sequence):
        self.sequence = sequence
        # Additional attributes and methods specific to DNA

# Define protein entities
ATM = Protein("ATM")
CDK = Protein("CDK")
CtIP = Protein("CtIP")
BRCA1 = Protein("BRCA1")
Ku80_Ku70 = Protein("Ku80-Ku70")
DNA_PKcs = Protein("DNA-PKcs")
Artemis = Protein("Artemis")
PNK = Protein("Polynucleotide Kinase (PNK)")
DNA_polymerase_X = Protein("DNA Polymerase X")
ligase_IV = Protein("Ligase IV")
Xrcc4 = Protein("Xrcc4")
Cernunos_Xlf = Protein("Cernunos/Xlf")

# Define DNA entities
target_sequence = "ACGTGCAGCTGGGTGGTTGTGGTTTGCTTGGCTTGAGAAGCAGGTTAAGCTGGTGGCTTGA"
dsb_site = DNA(target_sequence)

# Function to design a gRNA for a target sequence
def design_gRNA(target_sequence):
    # Find a suitable gRNA sequence
    gRNA = None
    for i in range(len(target_sequence) - 20):
        candidate_gRNA = target_sequence[i:i + 20]
        if MeltingTemp(candidate_gRNA) > 50.0 and BsmBI.search(candidate_gRNA) == []:
            gRNA = candidate_gRNA
            break
    return gRNA

# Design the gRNA
gRNA = design_gRNA(target_sequence)

# Define conditions X and Y based on gRNA presence
condition_X = bool(gRNA)  # HDR pathway enabled if gRNA is designed
condition_Y = not condition_X  # NHEJ pathway enabled if gRNA is not designed

# Simulation of HDR pathway
def perform_HDR():
    # Activation of ATM checkpoint
    ATM.phosphorylated = True
    print("ATM checkpoint activated.")

    # CDK-mediated phosphorylation of CtIP
    if ATM.phosphorylated:
        CtIP.phosphorylated = True
        print("CtIP phosphorylated by CDK.")

    # Formation of BRCA1-CtIP complex
    if CtIP.phosphorylated:
        BRCA1_CtIP_complex = [BRCA1, CtIP]
        print("BRCA1-CtIP complex formed.")

    # Additional steps and interactions specific to HDR
    # ...
```

```
    print("HDR pathway completed.")

# Simulation of NHEJ pathway
def perform_NHEJ():
    # Binding of Ku80-Ku70 heterodimer to broken DNA ends
    Ku80_Ku70_bound = True
    print("Ku80-Ku70 heterodimer bound to broken DNA ends.")

    # Recruitment of DNA-PKcs
    if Ku80_Ku70_bound:
        DNA_PKcs_bound = True
        print("DNA-PKcs recruited.")

    # DNA end processing steps
    if DNA_PKcs_bound:
        Artemis_processed = True
        PNK_processed = True
        DNA_polymerase_X_processed = True
        print("DNA ends processed by Artemis, PNK, and DNA Polymerase X.")

    # DNA end ligation
    if Artemis_processed and PNK_processed and DNA_polymerase_X_processed:
        ligase_IV_bound = True
        Xrcc4_bound = True
        Cernunos_Xlf_bound = True
        print("DNA ends joined by Ligase IV with Xrcc4 and Cernunos/Xlf co-factors.")

    # Mutations in IDH1 gene caused by NHEJ pathway
    IDH1_mutated = True
    print("Mutations in IDH1 gene caused by NHEJ pathway.")

    # Effects of IDH1 mutations on cellular processes
    if IDH1_mutated:
        print("Effects of IDH1 mutations on cellular processes:")
        print("1. Production of abnormal isocitrate dehydrogenase (IDH) enzymes.")
        print("2. Generation of oncometabolite 2-hydroxyglutarate (2-HG).")
        print("3. Accumulation of 2-HG within cells.")
        print("4. Disruption of cellular pathways.")
        print("5. Competition with isocitrate in the TCA cycle.")
        print("6. Loss of function in wild-type IDH enzymes."
```

V. Ethical Consideration and Study Constrain

I. Ethical Consideration:

First of all, the study protocol and ethical considerations underwent rigorous review by the YSJ's Research Review Board. This board meticulously assessed the study design, methods, and data handling procedures to ensure strict adherence to ethical guidelines. Notably, the study obtained approval from the aforementioned board prior to the commencement of data collection, thus safeguarding the rights and welfare of the participants.

As for ethical considerations, the data we have collected is among the precursors of ethical consideration in peer review. Additionally, all sources are mentioned to ensure credibility. In terms of transparency, since our research paper is theoretical in nature, we employed a specific methodology, which involved collecting data from books and prior articles. We then analyzed this data to identify connections between gene editing and mental health. Subsequently, we modeled the relationship between the CRISPR-Cas9 method and its influence on the IDH1 gene, which is responsible for brain cancer. In the discussion section, we outlined potential cures for these conditions.

When it comes to the ethical considerations surrounding gene editing, particularly in the context of human genome editing, have sparked intense debate and led to the formulation of guidelines and regulations. The advent of CRISPR technology, with its potential for precise genetic modifications, has amplified these discussions.

One central concern is safety. The risk of unintended off-target effects and mosaicism poses significant challenges. Many experts agree that, until germline genome editing is proven safe through rigorous research, it should not be employed for clinical reproductive purposes. Some argue that existing technologies like preimplantation genetic diagnosis (PGD) and in-vitro fertilization (IVF) offer safer alternatives for preventing genetic diseases.

However, exceptions are acknowledged. Germline editing might be justified when both prospective parents carry disease-causing variants or for addressing polygenic disorders. The balance between therapeutic use and potential misuse, such as for non-therapeutic enhancements, remains a subject of ethical debate.

Informed consent is another complex issue. Obtaining informed consent for germline therapy is challenging since the affected individuals are embryos and future generations. Nonetheless, proponents argue that parents routinely make decisions affecting their future children, including those related to PGD and IVF.

Justice and equity concerns arise as well. Gene editing's accessibility could exacerbate existing healthcare disparities and create genetic privilege. To prevent such outcomes, ethical guidelines and regulations must be established.

Regarding genome-editing research involving embryos, moral and religious objections exist, and federal funding restrictions apply in the United States. Nevertheless, some consider such research important for advancing scientific understanding. Research on nonviable embryos and viable embryos under certain conditions has been permitted in some countries, each with its own moral considerations.

ii. Study Constrains:

The study constraints of our paper were significant. Owing to limited resources and time constraints, the designated period for data collection was confined to a mere two weeks, with only seven weeks allocated for the entire research paper. This predicament imposed inherent limitations regarding the recruitment of methods and the extent of data analysis that could be undertaken. Furthermore, financial constraints significantly impacted access to advanced tools and equipment. As our research couldn't utilize advanced model applications or laboratory facilities for monitoring the gene editing process, the limitations of resources posed a considerable challenge. Additionally, gene editing methods are relatively new and complex, further exacerbating these challenges.

VI. Discussion

i. The Findings:

We initiated our research paper by addressing the challenges associated with gene editing, DNA transcription, translocation, and mental health disorders. We embarked on a comprehensive review of prior articles, focusing on the impact of gene editing on DNA transcription and translocation, as well as its influence on mental health.

Our research journey involved delving into review books such as 'Principles of Genetics'[42], 'Genetics of Mental Disorders' [43], and 'Editing Humanity' [44]. These sources provided valuable insights into the complex interplay between genetics, mental health, and the implications of gene editing.

As we delved deeper into our investigation, we unraveled the critical role of DNA repair mechanisms, particularly

nonhomologous end joining (NHEJ), as discussed in Section III. Notably, our research highlighted the occurrence of errors in the final steps of NHEJ, which hindered the formation of ligase due to the absence of a template.

Building on these findings, we proceeded to model the processes involved and, based on our analysis, proposed potential cures, as elucidated in Subsection II. Our research seeks to shed light on the intricate relationship between gene editing and its impact on mental health, ultimately aiming to contribute to advancements in addressing these complex challenges.

ii Thermotical Potential Cure:

In the first step, we will monitor the process to allow us to understand the activity of the CRISPR-Cas9 method on IDH1, using it as an example to simulate these steps. Monitoring by using Bioluminescence Imaging is useful. What makes BLI exceptionally useful is its capacity for real-time tracking and visualization of CRISPR-Cas9-induced changes. It enables researchers not only to observe genetic modifications as they happen but also to quantify their intensity. This real-time aspect can be invaluable for assessing the efficiency and specificity of gene editing processes. Researchers can use BLI to monitor changes over time, gaining insights into the dynamics of gene editing within living organisms. Moreover, BLI is non-invasive, minimizing disruptions to the biological system under investigation, and it can provide longitudinal data, allowing for the assessment of gene-editing persistence. It's an elegant and comprehensive approach for studying the in vivo impacts of CRISPR-Cas9 technology.

The process begins by meticulously selecting or designing a bioluminescent reporter that aligns with the IDH1 gene's genomic region of interest. This reporter is thoughtfully constructed to incorporate a gene encoding a light-emitting protein, such as firefly luciferase. The choice of this reporter gene is critical because it will act as a beacon, emitting light in response to any genetic changes initiated by CRISPR-Cas9 within the IDH1 gene.

Once the bioluminescent reporter is crafted, it undergoes genetic modification to ensure that it integrates seamlessly into the genomic landscape surrounding the IDH1 gene. This integration is achieved using tailored techniques like viral vectors or direct transfection, ensuring that the reporter becomes an integral part of the IDH1 gene environment.

With the bioluminescent reporter now strategically placed within the IDH1 gene's vicinity, the next step involves introducing the CRISPR-Cas9 system, guided by a gRNA molecule, into the target cells. The primary objective is to enable this system to initiate precise double-strand breaks (DSBs) at predetermined sites within the IDH1 gene. These DSBs are strategically chosen to correspond to specific regions of interest within the IDH1 gene, allowing researchers to monitor changes in these regions with precision.

The hallmark of BLI's utility in this context lies in its ability to exploit the cellular repair mechanisms, notably the Non-Homologous End Joining (NHEJ) pathway. When DSBs occur within the IDH1 gene, the cellular repair machinery, including NHEJ, springs into action. NHEJ's role is to mend these breaks, but it is known for its potential to introduce errors during the repair process.

In the case of the IDH1 gene, NHEJ might inadvertently disrupt the integrated bioluminescent reporter gene, leading to a reduction in bioluminescence. This reduction serves as a real-time indicator of CRISPR-Cas9 activity specifically within the IDH1 gene. It allows to monitor and quantify the impact of gene editing on the IDH1 gene in living organisms, offering invaluable insights into the dynamics of this process and its potential therapeutic application.

iii. DNA Ligation:

As the error occurs in the final steps of DNA ligation, as shown in figure 6 , in NHEJ, involving a ligase enzyme encoding ligase enzymes into cells to correct genetic defects will be beneficial. This correction process can be monitored by BLI, allowing for the detection of the time of ligation

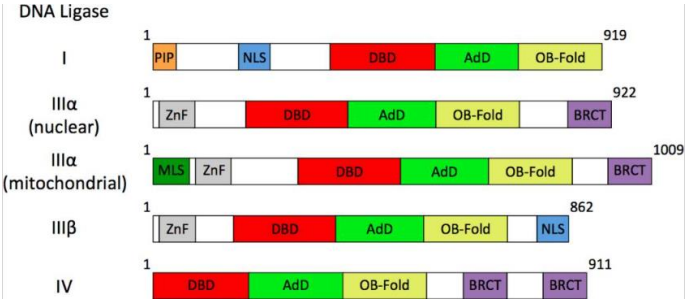

Figure 6 show DNA ligation [45]

The process of introducing specific genes, including those encoding ligase enzymes, into cells to correct genetic defects or enhance cellular functions involves a series of well-defined steps. This approach holds great promise for addressing genetic abnormalities like the IDH1 gene, as mentioned in the research paper. To begin, DNA ligases play a pivotal role in this process by catalyzing the formation of phosphodiester bonds, which are essential for sealing nicks in DNA strands. In humans, three genes encode different DNA ligase enzymes: DNA ligase I, III, and IV. These enzymes function in various cellular processes, including DNA replication, repair, and maintenance.

The first step in introducing specific genes is the preparation of the target cells. These cells are typically cultured and prepared for gene delivery. The next step involves the creation of the desired genetic construct, which may include the gene of interest, regulatory elements, and the ligase enzyme gene. This construct is then introduced into the target cells using techniques like transfection, viral vectors, or electroporation. Once inside the cells, the DNA ligase enzyme encoded by the introduced gene becomes active. The ligase functions by first activating ATP, resulting in the covalent linkage of an AMP moiety to a specific lysine residue within the enzyme's active site. This step is followed by the transfer of the AMP moiety to the 5' terminus of a DNA nick, creating a DNA-adenylate intermediate. Finally, the DNA ligase catalyzes the formation of a phosphodiester bond, sealing the nick in the DNA strand and releasing AMP [45].

This process of introducing specific genes, along with the ligase enzymes, offers immense potential for addressing genetic defects like the IDH1 gene mutation. By precisely delivering corrected genes or enhancing cellular functions, our researcher aims to develop innovative therapies for a wide range of genetic mental health disorder disorders. Furthermore, the use of bioluminescence imaging (BLI) techniques can help monitor the success and progress of gene delivery and expression within target cells, ensuring the effectiveness of this approach.

VII. Conclusion and Recommendation

In this research paper, we have embarked on a comprehensive journey to explore the intricate relationship between gene editing, DNA transcription, translocation, and their impact on mental health in adults aged 18 and above. Our study's primary objectives were to shed light on this underexplored area of research and propose potential therapeutic interventions. We have made several noteworthy contributions, including our focus on the adult demographic, our emphasis on the connection between gene editing and mental health through DNA processes, and our utilization of computational biology for modeling and analysis.

Two prominent gene-editing technologies, CRISPR-Cas9 and TALENs, have been discussed in detail. The CRISPR-Cas9 system's precision in directing Cas9 to target DNA sequences and the influence of TALENs on gene editing have been highlighted. We have elucidated the potential errors occurring in the final steps of Non-Homologous End Joining (NHEJ), which can result in gene disruptions and mutations. These disruptions can impact key gene functions related to neurotransmitter regulation, brain development, and mental health conditions.

Homology-Directed Repair (HDR), a more accurate but slower repair pathway, has also been explained. The significance of HDR in making precise DNA sequence changes and the potential for errors during the process have been discussed. These errors can lead to functional alterations with direct implications for neural processes and mental health.

To address the impact of gene editing on mental health, we have proposed a computational methodology using the Python language and the Biopython library. Our modeling focuses on the CRISPR-Cas9 method's activity on the IDH1 gene, which is responsible for brain cancer. The real-time monitoring of this process through Bioluminescence Imaging (BLI) offers a valuable tool for assessing gene editing efficiency and specificity.

Additionally, we have highlighted the importance of DNA ligation in correcting genetic defects of the gene editing . DNA ligases, including DNA ligase I, III, and IV, play a crucial role in sealing nicks in DNA strands. The process of introducing genes encoding ligase enzymes into cells to correct genetic defects has been outlined. Monitoring this correction process by BLI allows for the precise detection of the time of ligation.

In conclusion, this research paper has contributed to a deeper understanding of how gene editing processes impact DNA transcription, translocation, and mental health, especially in the context of errors occurring in NHEJ. By utilizing computational biology and innovative techniques like BLI, we aim to propose potential therapeutic interventions for genetic mental health disorders. Our paper has successfully added new information to the literature. Our research significantly contributes to the existing body of knowledge by delving into the intricate relationship between gene editing, DNA transcription, translocation, and their impact on mental health in adults aged 18 and above. Ethical considerations surrounding gene editing have also been discussed, emphasizing the need for safety, informed consent, justice, and equity in genetic research.

For further researchers, we recommend:

Addressing Limitations: It's crucial for future studies to acknowledge and work within the limitations we have outlined in our research. Limited resources, time

constraints, and the complexity of gene editing methods can pose challenges. Researchers should carefully plan their studies, allocate adequate resources, and manage time effectively to overcome these constraints.

Exploring Potential Cures: The potential therapeutic interventions we have proposed, such as monitoring gene editing with Bioluminescence Imaging (BLI) and introducing genes encoding ligase enzymes for DNA ligation, should be further investigated. Researchers should conduct in-depth studies to validate the effectiveness of these interventions in correcting genetic defects related to mental health disorders.

Utilizing Professional Equipment: To ensure the accuracy and reliability of research findings, it is essential for future researchers to employ professional equipment and state-of-the-art technologies. Two notable examples of such equipment include high-resolution microscopes with live-cell imaging capabilities and advanced gene editing platforms like CRISPR-Cas9 systems. These tools can provide precise data and insights necessary for groundbreaking discoveries in the field.

These recommendations encompass the need to overcome limitations, delve deeper into potential cures, and utilize advanced equipment, all of which can collectively contribute to advancing our understanding of gene editing's impact on mental health and the development of effective therapeutic interventions.

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