Narrative Review Article

CRISPR Therapies in Treating Monogenic Neurodevelopmental Disorders

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ABSTRACT

Neurodevelopmental Disorders (NDDs) arise when a pathogenic gene mutation disrupts an individual's brain development, often resulting in symptoms such as epilepsy, motor impairments, and intellectual disability. Historically, NDDs have been managed primarily through pharmacological and behavioral therapies that alleviate symptoms but do not address the underlying genetic causes. Recent advances in genomic medicine, particularly the development of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based technologies, have created the opportunity to directly target disease-causing genes. The versatility of CRISPR has enabled the development of multiple editing and regulatory modalities, allowing increasingly precise control of gene expression. Preclinical studies in rodent models suggest that CRISPR-mediated epigenetic reactivation may be an effective strategy for treating monogenic NDDs by restoring gene function without permanently altering the DNA sequence. While these approaches show promise, significant challenges related to delivery, safety, and ethical considerations remain. Despite these controversies surrounding the use of CRISPR, it remains a prospective candidate in improving the management of NDDs in the future. This review evaluates the potential of CRISPR-based editing as a therapeutic strategy for monogenic NDDs and evaluates the limitations that must be addressed before its widespread application in human patients.

Keywords: Neurodevelopmental Disorders; Monogenic Conditions; CRISPR/Cas9; Gene Regulation; Gene Editing

INTRODUCTION

Neurodevelopmental disorders (NDDs) are conditions that disrupt typical brain development and can lead to symptoms such as epilepsy, intellectual disability, communication difficulties, movement disorders, and behavioral challenges. Common examples include Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD), which affect approximately 0.76% and 7.6% of adolescents, respectively (1,2). Beyond clinical symptoms, individuals with NDDs often experience social difficulties, reduced independence, and increased vulnerability to comorbid mental health conditions. Although environmental factors can influence brain development, genetic factors are a major driver of many NDDs, particularly rare and severe forms (3). Traditional treatment strategies, such as behavioral therapies and pharmacological therapies, can help temporarily manage individual symptoms but fail to address the root cause of the condition. For example, antiepileptic drugs can reduce the frequency of seizures and physiotherapy may support motor function, but these approaches do not correct the genetic abnormalities that give rise to NDDs. This therapeutic gap highlights the

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Accepted June 29, 2026
https://doi.org/10.70251/HYJR2348.443240

need for disease-modifying strategies that directly target the genetic origins of these conditions.

Recent advances in gene editing technologies, particularly Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), have made it possible to modify genes with increasing precision (4). The CRISPR system was first identified in bacteria as part of an adaptive immune system against viral infection. Following viral exposure, bacteria incorporate fragments of viral DNA in CRISPR loci within their genome, allowing them to recognize the virus upon subsequent encounters. During re-exposure, RNA molecules derived from these loci guide CRISPR-associated (Cas) proteins, such as Cas9, to complementary viral DNA sequences, which are then cleaved and inactivated. Biochemists Jennifer Doudna and Emmanuelle Charpentier were able to reproduce this process in vitro by engineering a single guide RNA (gRNA) capable of directing Cas9 to specific DNA targets (5). Their discovery transformed CRISPR from a natural immune mechanism into a programmable gene-editing tool, allowing targeted modification of genetic material. Despite its efficiency, versatility, and relative cost-effectiveness, several challenges currently limit its clinical application. These include off-target effects, immune responses to CRISPR components, delivery-related limitations, and ethical considerations (6). Off-target effects occur when Cas9 induces unintended DNA breaks at non-target genomic sites, potentially leading to additional mutations and cellular dysfunction. Furthermore, delivering CRISPR components to specific tissues remains a significant obstacle. While some tissues, such as the eye, are relatively accessible, others, including the brain, have substantial anatomical and biological barriers. In addition, ethical concerns regarding the responsible use of CRISPR also persist. Nevertheless, CRISPR remains a highly promising therapeutic strategy for the treatment of genetic diseases.

Because of its capacity to directly target disease-causing mutations, genomic medicine represents a particularly attractive therapeutic approach for NDDs. Although NDDs can vary widely in complexity, aetiology, and clinical presentation, CRISPR-based interventions show the greatest potential for rare monogenic forms of these disorders. While common NDDs are typically multifactorial, involving the interaction of multiple genetic and environmental factors, a substantial portion of rare and severe NDDs arise from mutations in a single gene. With monogenic disorders contributing to up to 50% of cases of intellectual disability, advances in genomic therapies have the potential to significantly impact patient outcomes (7).

The clinical potential of CRISPR technology has already been demonstrated in non-neurological contexts. Researchers at the Children's Hospital of Philadelphia (CHOP) successfully corrected a pathogenic mutation responsible for a lethal metabolic disorder in an infant by administering a personalized lipid-based editing therapy during the first year of life (8). The patient showed a positive response to treatment and is currently thriving. In addition, CRISPR-based therapies are being actively explored for genetic disorders affecting the blood, eyes, and liver (9). As scientists take the next steps to safely expand CRISPR's capabilities to the brain, genomic medicine emerges as a compelling therapeutic approach for individuals living with monogenic NDDs.

This review aims to evaluate current advances in the application of CRISPR-Cas9 gene-editing technology in the context of rare monogenic NDDs, while providing an overview of the challenges that still limit its clinical application, including safety, delivery, and ethical considerations.

CRISPR STRATEGIES FOR MONOGENIC NDDS

Because monogenic NDDs arise from pathogenic mutations in a single gene, they present a clear opportunity to target the underlying genetic cause using CRISPR/Cas9 (Figure 1). Examples include Rett syndrome, Fragile X syndrome, Angelman syndrome, and Dravet syndrome, among many others. These disorders were included to portray different levels of preclinical and translational development in gene-targeted therapies for monogenic NDDs. Dravet syndrome and Angelman syndrome were selected since they have relatively strong CRISPR-based preclinical evidence in animal models, while Rett syndrome effectively highlights the difficulty of precisely modulating gene expression in a dosage-sensitive disorder. *SLC6A1*-related neurodevelopmental disorder is much rarer compared to these other conditions, but was included as a clinically relevant example of a monogenic NDD advancing toward early human gene therapy studies. Collectively, each monogenic NDD demonstrates the promise and limitations of translating gene-targeted therapies from experimental models to clinical application, situated in different contexts (Table 1). Although each of these conditions is individually rare, pathogenic variants in single genes are a well-

Table 1. Gene-targeted therapeutic approaches for selected monogenic neurodevelopmental disorders. *Summary of the principal molecular defect, therapeutic strategy, and current developmental stage for selected monogenic neurodevelopmental disorders discussed in this review. Approaches include CRISPR-mediated transcriptional activation or derepression, gene replacement, and other gene-regulatory strategies. Most remain supported primarily by preclinical animal and/or cellular studies, whereas SLC6A1-related neurodevelopmental disorder illustrates early clinical translation of a gene-targeted therapy.*

Disorder	Gene	Main molecular problem	Therapeutic strategy discussed	Evidence/stage
Dravet syndrome	SCN1A	Haploinsufficiency / reduced Nav1.1 expression	CRISPRa / dCas9-mediated transcriptional activation	Preclinical mouse studies
Angelman syndrome	UBE3A	Loss of maternal UBE3A expression; paternal allele silenced by UBE3A-ATS	CRISPR-mediated targeting of UBE3A-ATS	Preclinical mouse studies
Rett syndrome	MECP2	MECP2 haploinsufficiency; dosage-sensitive gene	Gene replacement / RNA or CRISPR-based regulation	Mostly preclinical and in vitro evidence
SLC6A1-related NDD	SLC6A1	Reduced GABA transporter function	AAV-mediated gene replacement / gene-targeted therapy	Early clinical translation

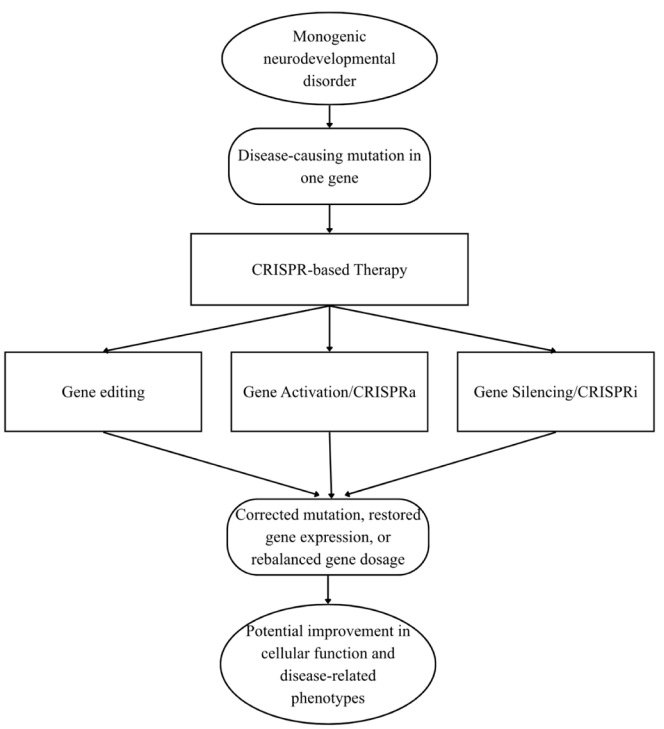

Figure 1. Overview of CRISPR-based therapeutic strategies for monogenic neurodevelopmental disorders. *In monogenic NDDs, a pathogenic variant in a single gene can disrupt gene function or expression. CRISPR-based approaches may act through direct gene editing, transcriptional activation using CRISPRa, or gene repression using CRISPRi. Depending on the disorder, these strategies aim to correct the mutation, restore gene expression, or rebalance gene dosage, potentially improving disease-related cellular and clinical phenotypes.*

established cause of intellectual disability and related neurodevelopmental phenotypes (7). At present, there are no approved treatments that address the core molecular pathology of monogenic NDDs. However, a growing body of evidence from *in vitro* studies using patient-derived human induced pluripotent stem cells (iPSCs) and *in vivo* studies in animal models suggests that correcting or compensating for disease-causing variants may be feasible (10,11). iPSC-based disease models allow researchers to assess the therapeutic efficacy and long-term safety in a human cellular context without direct risk to patients. In these systems, somatic cells obtained from affected individuals are reprogrammed into iPSCs and then differentiated into relevant cell types, including neural ones. This provides an important platform for testing gene-editing approaches and supports the development of more personalized genomic therapies (12).

In vivo mouse models have further demonstrated the therapeutic potential of CRISPR-based interventions for monogenic NDDs, including Dravet syndrome, one of the most well-studied monogenic NDDs (13). Dravet syndrome is caused by haploinsufficiency of the *SCN1A* gene, in which one allele is nonfunctional, leading to reduced expression of the Nav1.1 sodium channel. This deficit results in severe, early-onset epilepsy that is often refractory to conventional antiepileptic drugs and can be life-threatening. Building on findings from iPSC-based studies, researchers developed a CRISPR activation (CRISPRa or "CRISPR-ON") strategy to increase endogenous *SCN1A* expression in *Scn1a*-deficient

mice. This approach used a catalytically inactive Cas9 (dCas9) fused to transcriptional activators, delivered alongside guide RNAs via an adeno-associated virus (AAV) vector. Following systemic administration of the therapy in the early postnatal period, treated mice exhibited a significant increase in *SCNA1* expression, accompanied by reductions in seizure frequency and intensity. Behavioral improvements were also observed, including increased exploratory activity and lower anxiety levels, approaching levels seen in wild-type mice. These findings suggest that epigenetic upregulation of a haploinsufficient gene could be an effective way to treat certain monogenic NDDs, even without directly correcting the underlying mutation. Nevertheless, these improvements are considered moderate, and more research is necessary to minimize health risks and allow clinical translation (14).

Angelman syndrome provides another example of a monogenic NDD in which CRISPR-based gene regulation strategies show promise. This disorder is caused by loss of function of the maternally inherited *UBE3A* allele, resulting in haploinsufficiency and leading to symptoms such as epilepsy, intellectual disability, and ataxia (15). Rather than directly activating the silenced maternal allele, current CRISPR approaches aim to restore UBE3A expression by targeting UBE3A-antisense transcript (UBE3A-ATS), a long non-coding RNA that represses expression of the paternal UBE3A allele. By disrupting UBE3A-ATS, paternal UBE3A expression can be reactivated without permanently altering the DNA coding sequence, potentially reducing safety concerns. In a study using mouse models of Angelman syndrome, CRISPR-mediated disruption of UBE3A-ATS using AAV delivery resulted in reactivation of paternal UBE3A expression and partial correction of disease-associated phenotypes. Neonatal mice that received the intraventricular (i.c.v.) injection responded well to the treatment, experiencing no treatment-related mortalities and showing drastic improvements in behavior and motor function. They found that i.c.v. injection in a neonatal mouse brain was most effective compared to intravenously administering the treatment in later brain development stages. While neonatal intraventricular administration has limited direct clinical applicability, given that most human diagnoses occur after symptom onset, these findings provide valuable insight into the biology of Angelman syndrome and the therapeutic potential of CRISPR/Cas9 (16).

Rett syndrome represents another monogenic NDD caused by haploinsufficiency of the MECP2 gene and is characterized by epilepsy, autistic features, motor impairment, and ataxia (17). Unlike many other monogenic disorders, Rett syndrome predominantly affects females due to the gene's location on the X chromosome and the effects of X-chromosome inactivation. Therapeutic strategies for Rett syndrome are particularly challenging, as both insufficient and excessive *MECP2* expression can result in severe neurological dysfunction (18). An early landmark preclinical study demonstrated that restoring MECP2 expression to physiologically appropriate levels could reverse Rett syndrome-like phenotypes in both juvenile and adult mice (19). This was the first evidence that neurodevelopmental disorders are not necessarily irreversible. Although it has been proven that restoring MECP2 expression in adult mice can reverse the phenotypic effects of Rett syndrome, this experiment only provided proof of principle (19). More recent work has explored multiple approaches to modulating MECP2 expression, including gene replacement, RNA editing, and CRISPR-based regulation. While relatively few studies have applied CRISPR-Cas9 directly to Rett syndrome models in vivo, extensive in vitro experiments using human iPSCs suggest that CRISPR-based strategies could represent a viable therapeutic option if precise control of gene dosage can be achieved (20). Determining safe and effective methods to regulate MECP2 expression remains a major challenge in the field.

Beyond preclinical models, various studies conducted over the past few years have contributed toward the clinical application of CRISPR gene therapy for rare monogenic NDDs. Recently, researchers at SLC6A1 Connect and Nationwide Children's worked together to develop an experimental gene therapy for SLC6A1-related neurodevelopmental disorder, which causes symptoms like autism, ataxia, and epilepsy, similar to other monogenic NDDs (21). The gene therapy was developed by modulating the gene expression of SLC6A1 and observing the phenotypic results in mice. The therapy was developed through extensive in vitro and in vivo testing to assess efficacy and safety prior to regulatory approval. Following approval by the US Food and Drug Administration (FDA), the treatment was delivered using an AAV9 vector, which has enhanced tropism for the central nervous system and can cross the blood-brain barrier. Rather than intravenous administration, the therapy was delivered directly into the cerebrospinal fluid to improve central nervous system targeting and reduce systemic exposure.

The first in-human administration occurred in

September 2025 when the treatment was delivered to an 8-year-old boy with *SLC6A1*-related condition, marking a turning point in using gene therapy for neurodevelopmental disorders. Early reports indicate a favorable response; however, long-term monitoring is required to fully evaluate the safety, durability, and efficacy of the treatment (22). After successfully developing two of the first eight FDA-approved gene therapies, researchers at Nationwide Children's Hospital are already renowned for producing effective gene-based treatments. With institutional support from external organizations and other resources, the treatment for SLC6A1 seems to be a promising model for effectively treating monogenic NDDs (23).

Overall, current evidence suggests that CRISPR-based approaches are best suited for treating monogenic NDDs through strategies such as gene reactivation, gene replacement, or transcriptional regulation. These approaches are highly adaptable, demonstrate consistent efficacy in iPSC models, and produce measurable phenotypic improvements in animal studies. However, given the heterogeneity of monogenic NDDs, tailored therapeutic strategies will be required for each condition. A thorough understanding of optimal delivery methods, gene dosage sensitivity, and disease biology will be essential to ensure the safe and effective clinical application of CRISPR-based therapies for NDDs.

CHALLENGES AND CONSIDERATIONS FOR CLINICAL TRANSLATION

Despite its considerable therapeutic potential, CRISPR-based treatment for monogenic NDDs faces several technical, biological, and ethical challenges that currently limit its clinical application.

One of the most significant obstacles to applying CRISPR therapies for NDDs is effective delivery to the central nervous system, largely due to the presence of the blood-brain barrier (BBB). The BBB restricts the passage of large biomolecules, making systemic delivery of gene-editing tools to the brain inefficient (24). Direct delivery approaches, such as intracerebroventricular (ICV) injection in combination with viral vectors, have been explored as a means of bypassing the BBB. ICV administration introduces CRISPR components directly into the cerebrospinal fluid, facilitating their distribution throughout the brain. While this strategy has demonstrated efficacy in preclinical models, it is considerably more invasive than systemic delivery and presents challenges for widespread clinical use, particularly in pediatric patients.

While iPSC-derived neural models are valuable platforms for evaluating therapeutic efficacy in a human cellular context, they have some limitations that need to be accounted for. iPSC models do a good job at modelling NDDs in a controlled setting, but on a small scale. Consequently, they are not able to encapsulate complex in vivo neural circuits with complete accuracy. Similarly, they do not capture the effects of developmental timing, meaning that the results of an edit can vary based on the gene's role during different stages of development. Cells also do not always develop the same during the reprogramming and differentiation process. This introduces a slight variability in the iPSCs and neurons, which may affect experimental results. Because of these factors, promising results in editing iPSCs may not always reflect the conditions of a human brain.

Viral vectors, particularly AAVs, are currently the most widely used vehicles for delivering CRISPR components to neural tissue. AAVs are genetically engineered to remove pathogenic genes, allowing them to efficiently infect target cells while generally eliciting relatively low immune responses (25). In rodent models, engineered AAVs have shown strong tropism for neurons and effective CNS transduction following ICV delivery. However, differences between rodent and human BBB physiology raise concerns about the translatability of these findings. Beyond these differences in the BBB, other factors can create challenges for mouse to human translation and should be considered. The human brain is notably larger and more complex than the rodent brain, for example, which may result in ineffective transduction in a clinical setting. Differences in neuronal density and glial composition can impact this as well and further influence brain development, myelination, synapse formation, and immune responses. Brain development happens more rapidly in mice, which can affect the intervention timing in humans for maximum treatment efficiency. Myelination in rodents to humans also differs in terms of onset, duration, and complexity, which can determine symptom development and treatment effectiveness. Additionally, the rodent and human immune systems mature differently and can elicit different responses to viral vectors and CRISPR proteins. Given these contrasts, successful treatment results in mice should be viewed as promising preclinical evidence rather than an indication that a therapy is best suited for humans. Furthermore, multiple vector-related factors, including serotype selection, dose, immune response, and tissue distribution, significantly influence

therapeutic efficacy (20). A major limitation of AAV-based delivery is its restricted cargo capacity of about 5.0 kb. This can complicate the delivery of CRISPR components, particularly when larger Cas enzymes or multiple regulatory elements are required. For this reason, strategies such as split-Cas systems, smaller Cas variants, or transcriptional regulation approaches are often necessary. Serotype selection also plays a critical role: AAV9 is frequently used in animal studies due to its ability to cross the BBB and target the CNS in rodents, yet emerging evidence suggests that this efficiency may not be replicated in humans. Although AAVs are generally considered to have low immunogenicity, high-dose administration can trigger immune responses, including neutralising antibodies that reduce transduction efficiency and, in severe cases, induce systemic immunotoxicity. Lower dosing may reduce immune-related toxicity but can compromise therapeutic durability and efficacy. Determining an optimal balance between safety and effectiveness remains a major challenge for clinical translation (26).

In addition to vector-related immunity, immune responses to CRISPR-associated proteins themselves present further concerns. Pre-existing humoral and cellular immunity to commonly used Cas9 enzymes derived from Staphylococcus aureus (SaCas9) and Streptococcus pyogenes (SpCas9) has been detected in human populations. These immune responses could reduce treatment efficacy or lead to adverse effects. To mitigate this risk, protein engineering approaches aimed at reducing Cas9 immunogenicity have shown promise (27), as has the development of "deimmunised" Cas9 (28). Although these modifications can help make CRISPR/Cas9-based therapies safer, patients must be monitored carefully and long-term due to the uncertainty surrounding delayed immune effects (4).

Off-target editing represents another major safety concern associated with CRISPR-Cas9 technology. Off-target effects occur when CRISPR components induce unintended DNA modifications at genomic sites with partial sequence similarity to the intended target, potentially resulting in deleterious mutations, loss of gene function, or oncogenic transformation (29). While some off-target edits may be biologically benign, their long-term consequences, particularly in tissues such as the brain, are difficult to predict. Given the critical role of neural circuits, unintended genomic alterations could lead to severe neurological complications. To address this risk, researchers are developing more precise guide RNAs, high-fidelity Cas9 variants, and computational tools that predict and screen for off-target sites. Advances in patient-specific genome analysis may further improve safety by tailoring CRISPR designs to individual genetic backgrounds (30).

Strategically planning when to administer treatment is also a key aspect of CRISPR-based therapies. Although CRISPR-based treatments can be effective in adult animal models, many studies suggest that early neonatal intervention yields better outcomes for CNS disorders (31). Administering treatment during embryonic or early postnatal development may allow broader neuronal transduction, exploit heightened neuroplasticity, and prevent the emergence of irreversible pathological features (32). However, the optimal therapeutic window varies across disorders and depends on disease severity, gene function, and treatment objectives. As such, careful evaluation of timing must be integrated into therapeutic design (33). Beyond technological challenges, a comprehensive understanding of the underlying biology of each monogenic NDD is essential for safe and effective treatment. Neurodevelopmental disorders differ widely in gene dosage sensitivity, cellular targets, and developmental trajectories. Insufficient knowledge of disease-specific mechanisms increases the risk of unintended neurological consequences following gene editing. Rare monogenic conditions, in particular, may suffer from limited research attention, making it difficult to design and evaluate tailored CRISPR interventions. The complexity of fully characterizing these disorders can slow therapeutic development and complicate risk-benefit assessments.

In addition to other risks, CRISPR therapies raise significant ethical concerns. Current clinical applications involve somatic gene editing, which is generally considered ethically permissible as the genetic modifications are confined to the treated individual. In contrast, germline editing, where genomic changes introduced at the embryonic stage can be inherited by future generations, remains highly controversial (34). Ethical challenges also arise in obtaining informed consent, particularly when treatment is administered in early childhood. Long-term follow-up requirements, uncertainty surrounding lifelong effects, and the inability of future generations to consent further complicate ethical decision-making.

Debates surrounding germline editing are often intensified by concerns about eugenics and social equity. While some geneticists argue for germline editing to prevent severe disease, defining what constitutes a "severe" condition is "inherently" subjective (35). The

potential elimination of traits associated with disability raises concerns about reduced neurodiversity and the reinforcement of harmful social norms. Furthermore, broader ethical considerations, including socioeconomic inequality, access to treatment, and legal regulation, must be addressed alongside scientific progress. Balancing the therapeutic promise of CRISPR with its ethical and societal implications underscores the need for robust ethical frameworks, transparent regulation, and sustained public engagement (36).

CONCLUSION

Neurodevelopmental disorders (NDDs) frequently originate from pathogenic gene mutations that disrupt typical brain development and function. The emergence of CRISPR/Cas9 gene-editing technology has introduced the possibility of directly targeting these underlying genetic causes, rather than merely managing symptoms. By enabling precise modification or regulation of disease-associated genes, CRISPR-based approaches represent a significant shift in the therapeutic landscape for genetic disorders.

Among the spectrum of NDDs, monogenic NDDs represent a particularly promising target for CRISPR-mediated intervention. Because these disorders result from mutations in a single gene, they offer a clearly defined target that is well-suited to gene-editing or gene-regulatory strategies. Approaches such as CRISPR-mediated transcriptional activation (CRISPR-ON) provide a means of restoring gene expression in conditions caused by haploinsufficiency without permanently altering the DNA sequence. Preclinical studies using iPSC-derived neural models and animal systems have demonstrated that such strategies can partially restore gene function and improve disease-associated phenotypes, highlighting their therapeutic potential.

Despite these advances, significant challenges remain before CRISPR-based therapies can be widely adopted in clinical practice. Technical barriers related to delivery, immune responses, off-target effects, and gene dosage control are particularly pronounced when targeting the central nervous system. In parallel, ethical concerns surrounding consent, long-term monitoring, and the broader societal implications of gene editing necessitate careful consideration. Addressing these challenges will require continued technological refinement, rigorous preclinical and clinical evaluation, and the development of robust ethical and regulatory frameworks.

Looking ahead, ongoing research aims to improve CRISPR/Cas9 technology, making it safer and more precise. Advances in vector engineering, immune modulation, and patient-specific genome analysis may further enhance therapeutic outcomes. Equally important will be sustained public engagement and interdisciplinary collaboration to ensure responsible implementation. While CRISPR technology is not yet ready for routine clinical use in neurodevelopmental disorders, its rapid evolution suggests a promising future in which genomic medicine may fundamentally transform the treatment of genetic brain disorders.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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