Exploring the Potential of CRISPR-Cas9 in Treating Neurodegenerative Diseases: Advances, Challenges, and Future Directions

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Neurological disorders, such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), and Amyotrophic Lateral Sclerosis (ALS), are increasingly prevalent, posing significant challenges due to their progressive nature and lack of curative treatments. Current therapeutic options primarily focus on symptomatic management rather than addressing the underlying causes of the disease. This review explores the emerging role of gene editing, particularly CRISPR-Cas9, as a potential therapeutic strategy for these disorders. CRISPR-Cas9 offers a precise method to target genetic mutations associated with neurodegeneration, potentially halting or reversing disease progression. The review delves into the applications of gene editing in PD, HD, AD, and ALS, highlighting the successes, challenges, and ethical considerations of this technology. While CRISPR-Cas9 presents promising therapeutic potential, significant obstacles remain, including delivery to the central nervous system, off-target effects, and ethical concerns surrounding germline editing. This review synthesizes current literature on CRISPR-Cas9 applications in neurodegenerative diseases, examines the mechanisms underlying gene editing, discusses disease-specific genetic targets, and evaluates the technical and ethical challenges of CRISPR-Cas9.

Introduction

Neurodegenerative diseases represent a growing global health crisis, affecting millions of individuals worldwide and placing substantial burdens on healthcare systems. Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), and Amyotrophic Lateral Sclerosis (ALS) are characterized by progressive neuronal loss, leading to debilitating motor and cognitive impairments[1]. Despite decades of research, current treatments remain largely palliative, offering symptomatic relief without addressing the underlying pathophysiology[2]. The genetic basis of many neurodegenerative disorders has been increasingly elucidated, revealing specific mutations that contribute to disease onset and progression[3]. This genetic understanding has paved the way for novel therapeutic approaches, including gene editing technologies. CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9) has emerged as a revolutionary tool in molecular biology, offering unprecedented precision in genome modification[4]. Originally discovered as a bacterial immune system, CRISPR-Cas9 has been adapted for mammalian genome editing, enabling researchers to correct disease-causing mutations, disrupt pathogenic gene expression, or insert therapeutic sequences[5]. The technology's simplicity, efficiency, and versatility have accelerated its application across various fields, including the treatment of genetic disorders[6].

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Mechanism of CRISPR-Cas9 Gene Editing

The mechanism of CRISPR-Cas9 gene editing relies on two key components: the Cas9 endonuclease and a guide RNA (gRNA). The gRNA is a synthetic RNA molecule approximately 20 nucleotides in length that is designed to be complementary to a specific DNA sequence in the genome[7]. This gRNA directs the Cas9 protein to the precise genomic location for editing. Once the gRNA-Cas9 complex binds to the target sequence, Cas9 acts as a pair of scissors, creating a double-strand break (DSB) at the specified site[8]. Following the DSB, the cell's endogenous DNA repair mechanisms are activated. The two primary repair pathways are non-homologous end joining (NHEJ) and homology-directed repair (HDR)[9,10]. NHEJ is an error-prone process that often results in insertions or deletions, which can disrupt gene function, which is helpful for gene knockout applications. In contrast, HDR is a more precise mechanism that uses a provided DNA template to repair the break, allowing the correction of mutations or the insertion of new genetic sequences[11]. The choice between these repair pathways depends on the cell cycle stage and the presence of a donor template, making the optimization of CRISPR-Cas9 delivery crucial for therapeutic applications.

Delivery Systems of CRISPR-Cas9

Delivering CRISPR-Cas9 components to target cells, particularly in the central nervous system (CNS), presents signifi-

cant technical challenges. Several delivery systems have been developed, each with distinct advantages and limitations. Viral vectors, particularly adeno-associated viruses (AAVs), are among the most widely used delivery vehicles for CRISPR-Cas9 in vivo[12]. AAVs offer several benefits, including low immunogenicity, broad tissue tropism, and the ability to transduce both dividing and non-dividing cells—a critical feature for targeting post-mitotic neurons[13]. However, AAVs have limited packaging capacity (approximately 4.7 kilobases), which can be restrictive when delivering the full-length Cas9 gene along with guide RNAs and regulatory elements[14]. To address this limitation, researchers have developed smaller Cas9 variants and split-AAV systems that deliver components across multiple viral particles[15]. Lentiviral vectors represent another viral delivery option, offering greater packaging capacity and stable genomic integration, but they carry higher immunogenicity risks and the potential for insertional mutagenesis[16]. Non-viral delivery methods, including lipid nanoparticles (LNPs), cell-penetrating peptides, and electroporation, have also been explored as alternatives to viral vectors[17]. LNPs, which have been successfully used for mRNA vaccine delivery, can encapsulate CRISPR-Cas9 ribonucleoprotein (RNP) complexes and protect them from degradation during systemic circulation[18]. A major obstacle to CNS delivery is the blood-brain barrier (BBB), a selective permeability barrier that restricts the passage of molecules from the bloodstream into the brain parenchyma[19]. Recent advances in BBB-penetrating delivery systems, including focused ultrasound-mediated BBB disruption and receptor-mediated transcytosis, show promise for improving CRISPR-Cas9 delivery to the brain[20].

This review examines the current state of CRISPR-Cas9 research in treating neurodegenerative diseases, with a focus on Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), and Amyotrophic Lateral Sclerosis (ALS). We explore disease-specific genetic targets, preclinical and clinical advances, and the technical and ethical challenges that must be overcome to realize the therapeutic potential of this technology.

Results

Parkinson's Disease (PD)

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by the progressive loss of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as tremor, rigidity, and bradykinesia[21]. While most PD cases are sporadic, approximately 10–15% have a genetic component, with mutations in several genes identified as causative or risk factors[22]. The most commonly implicated genes in familial PD include SNCA (α-synuclein), LRRK2 (leucine-rich repeat kinase 2), PARK2 (Parkin), PINK1 (PTEN-induced kinase 1), and DJ-1[23]. The SNCA gene encodes α-synuclein, a protein that misfolds and aggregates to form Lewy bodies, a pathological hallmark of PD[24]. Mutations in SNCA, including point mutations (A53T, A30P, E46K) and gene multiplications (duplications and triplications), lead to increased α-synuclein expression and enhanced aggregation propensity[25]. LRRK2 mutations, particularly the G2019S variant, are the most common genetic cause of PD, accounting for approximately 4% of familial cases and 1–2% of sporadic cases[26]. The G2019S mutation results in increased kinase activity, leading to neuronal dysfunction and death through mechanisms involving mitochondrial impairment and protein aggregation[27]. Loss-of-function mutations in PARK2, PINK1, and DJ-1 are associated with early-onset autosomal recessive PD and impair mitochondrial quality control pathways[28]. CRISPR-Cas9 has been applied to model PD in vitro and in vivo, as well as to develop potential therapeutic strategies. Researchers have used CRISPR to introduce PD-associated mutations into cellular and animal models, enabling the study of disease mechanisms[29]. In therapeutic applications, CRISPR-Cas9 has been employed to silence or reduce SNCA expression in models with gene duplications or triplications[30]. Studies have demonstrated that CRISPR-mediated reduction of α-synuclein levels can decrease protein aggregation and neuronal toxicity in both cell culture and animal models[31]. Similarly, CRISPR strategies targeting LRRK2 have focused on either correcting pathogenic mutations or reducing overall LRRK2 expression to mitigate the toxic gain-of-function effects associated with variants like G2019S[32]. One notable study used CRISPR-Cas9 to correct the LRRK2 G2019S mutation in patient-derived induced pluripotent stem cells (iPSCs), successfully reversing the pathological phenotype in differentiated dopaminergic neurons[33]. This proof-of-concept work demonstrates the potential for personalized gene editing approaches in PD. However, translating these findings to clinical applications faces significant hurdles, including the efficient delivery of CRISPR components to affected neurons in the adult brain and ensuring the safety of edited cells.

Huntington's Disease (HD)

Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disorder caused by an expansion of CAG trinucleotide repeats in the huntingtin (HTT) gene[34]. Individuals with 40 or more CAG repeats invariably develop HD, while those with 36–39 repeats have incomplete penetrance[35]. The expanded polyglutamine tract in the mutant huntingtin protein (mHTT) causes it to misfold and aggregate, leading to neuronal dysfunction and death, particularly in the striatum and cortex[36]. HD presents with a triad of motor, cognitive, and psychiatric symptoms, typically manifesting in mid-life and progressing over 15–20 years[37]. The genetic simplicity of

Table 1 Comparison of CRISPR-Cas9 Delivery Systems for CNS Applications

Parameter	AAV Vector	Lentiviral Vector	Lipid Nanoparticle (LNP)	Cell Penetrating Peptides	Electroporation
Payload Capacity	∼4.7 kb	∼9 kb	High	Limited	High
Immunogenicity	Low	Moderate–High	Low to Moderate	Low	Low
Targeting Efficiency	High	High	Moderate	Variable	Variable
Integration Risk	Very Low	Potential	None	None	None
Clinical Stage	Advanced	Moderate	Preclinical	Preclinical	Preclinical
Suitable for CNS?	Yes	Yes	Yes	Yes	Yes

HD—a single gene disorder with a known mutation—makes it an attractive target for gene editing therapies. CRISPR-Cas9 strategies for HD have focused on selectively inactivating or reducing the expression of the mutant HTT allele while preserving the wild-type allele[38]. Several approaches have been developed, including allele-specific targeting based on single-nucleotide polymorphisms (SNPs) linked to the expanded CAG repeat, as well as non-selective HTT reduction[39]. In preclinical studies, CRISPR-Cas9-mediated disruption of the HTT gene has shown promising results. Researchers have successfully reduced mHTT expression in HD mouse models and patient-derived cells, leading to decreased protein aggregation and improved cellular phenotypes[40]. One study demonstrated that AAV-mediated delivery of CRISPR-Cas9 targeting HTT in the striatum of HD mice resulted in reduced mHTT levels and improved motor function[41]. Another approach involves targeting the CAG repeat expansion itself, using CRISPR-Cas9 to excise the expanded repeat region or disrupt the repeat tract through NHEJ-mediated indels[42]. This strategy has shown efficacy in reducing toxic mHTT fragments and preventing neurodegeneration in animal models[43]. Despite these advances, challenges remain in achieving sufficient editing efficiency in the brain, minimizing off-target effects, and ensuring long-term safety. The dominantly inherited nature of HD also raises the question of whether partial reduction of mHTT is sufficient for therapeutic benefit or whether complete knockout is necessary.

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is the most common cause of dementia, affecting over 55 million people worldwide[44]. AD is characterized by progressive cognitive decline, memory loss, and behavioral changes, associated with the accumulation of amyloid-beta ($A\beta$) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein[45]. While most AD cases are late-onset and sporadic with complex genetic and environmental contributions, approximately 1–5% are early-onset familial AD (FAD) caused by autosomal dominant mutations[46]. The three genes primarily responsible for FAD are APP (amyloid precursor protein), PSEN1 (presenilin 1), and PSEN2 (presenilin 2)[47]. Mutations in APP lead to increased production or altered processing of $A\beta$ peptides, promoting their aggregation into neurotoxic oligomers and plaques[48]. PSEN1 and PSEN2 encode components of the γ-secretase complex, which cleaves APP to generate $A\beta$ peptides. Mutations in these genes cause aberrant γ-secretase activity, resulting in increased production of the highly aggregation-prone $A\beta 42$ isoform[49]. The most common PSEN1 mutations include E280A, M146L, and L286V, while PSEN2 mutations are less frequent but equally pathogenic[50]. CRISPR-Cas9 has been used to model FAD by introducing pathogenic mutations into cellular and animal models, facilitating the study of disease mechanisms and the testing of potential therapies[51]. Therapeutic applications of CRISPR-Cas9 in AD focus on correcting FAD-causing mutations in APP, PSEN1, or PSEN2 genes in patient-derived iPSCs[52]. Studies have demonstrated that correction of APP or PSEN1 mutations can normalize $A\beta$ production and reduce pathological features in neuronal cultures derived from gene-edited iPSCs[53]. Additionally, CRISPR has been employed to modulate genes involved in $A\beta$ clearance, such as APOE (apolipoprotein E), with the APOE4 allele being the strongest genetic risk factor for late-onset AD[54]. One innovative approach involves using CRISPR-Cas9 to convert the APOE4 allele to the less risky APOE3 variant in patient cells, which has shown promise in reducing AD-related pathology[55]. However, the sporadic and polygenic nature of most AD cases complicates the application of gene editing, as therapeutic strategies may need to target multiple genes or pathways simultaneously. The late-onset nature of AD also poses challenges for the timing of therapeutic intervention.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by the selective loss of motor neurons in the brain and spinal cord, leading to mus-

cle weakness, paralysis, and eventual respiratory failure[56]. Most ALS cases are sporadic (approximately 90%), while 10% are familial, with mutations in over 30 genes identified as causative or contributory[57]. The most commonly mutated genes in familial ALS include SOD1 (superoxide dismutase 1), C9ORF72 (chromosome 9 open reading frame 72), FUS (fused in sarcoma), and TARDBP (TAR DNA-binding protein 43)[58]. SOD1 mutations account for approximately 20% of familial ALS cases and 1–2% of sporadic cases[59]. Over 180 different SOD1 mutations have been identified, most of which cause disease through a toxic gain-of-function mechanism involving protein misfolding and aggregation[60]. The C9ORF72 hexanucleotide repeat expansion (GGGGCC) is the most common genetic cause of both ALS and frontotemporal dementia (FTD), accounting for approximately 40% of familial ALS and 7% of sporadic ALS cases[61]. The expanded repeat forms toxic RNA foci and produces dipeptide repeat proteins through non-canonical translation, both contributing to neurodegeneration[62]. Mutations in FUS and TARDBP disrupt RNA metabolism and lead to the formation of cytoplasmic protein aggregates, impairing cellular function[63]. CRISPR-Cas9 has been extensively used to develop ALS models and explore therapeutic strategies. Researchers have employed CRISPR to introduce disease-causing mutations into cell and animal models, enabling mechanistic studies and drug testing[64]. Therapeutic applications focus on silencing or correcting mutant SOD1 alleles, excising or disrupting the C9ORF72 repeat expansion, and modulating genes involved in RNA metabolism and protein homeostasis[65]. Studies have shown that CRISPR-mediated reduction of mutant SOD1 expression can slow disease progression and extend survival in ALS mouse models[66]. For C9ORF72-related ALS, CRISPR strategies have targeted the expanded repeat itself, using Cas9 to induce double-strand breaks that result in repeat contraction or excision through NHEJ repair[67]. This approach has demonstrated efficacy in reducing toxic RNA foci and dipeptide repeat proteins in patient-derived cells[68]. The heterogeneity of genetic causes in ALS presents a challenge for developing universal gene editing therapies, as treatments may need to be tailored to specific mutations. Additionally, the progressive and often rapid course of ALS necessitates early intervention, which requires reliable biomarkers for disease detection and monitoring.

Table 2 Key Genetic Targets in Neurodegenerative Diseases

Disease	Key Gene Targets	Mutation Type
Parkinson's Disease (PD)	SNCA, LRRK2, PARK2	Point mutation and gene duplications
Huntington's Disease (HD)	HTT	CAG repeat
Alzheimer's Disease (AD)	APP, PSEN1, PSEN2	Gene duplications and missense mutations
Amyotrophic Lateral Sclerosis (ALS)	SOD1, C9orf72, TARDBP, FUS	Repeat expansion and missense mutations

Challenges and Limitations

Off-Target Effects

One of the most significant concerns with CRISPR-Cas9 gene editing is the potential for off-target effects, where the Cas9 endonuclease cleaves DNA at unintended genomic sites that share sequence similarity with the target site[69]. Off-target editing can lead to unintended mutations, chromosomal rearrangements, or disruption of essential genes, potentially causing cellular dysfunction or oncogenic transformation[70]. The specificity of CRISPR-Cas9 is primarily determined by the sequence of the gRNA, which typically requires a 20-nucleotide target sequence adjacent to a protospacer adjacent motif (PAM)[71]. However, Cas9 can tolerate mismatches between the gRNA and the target DNA, particularly in the PAM-distal region, leading to off-target cleavage[72]. Multiple strategies have been developed to minimize off-target effects and enhance the precision of CRISPR-Cas9 editing. High-fidelity Cas9 variants, such as SpCas9-HF1, eSpCas9, and HypaCas9, have been engineered to reduce non-specific DNA binding and improve on-target specificity without compromising editing efficiency[73]. These variants contain mutations in the Cas9 protein that weaken interactions with the DNA backbone, making the enzyme more stringent in its target recognition[74]. Another approach involves using truncated gRNAs (17–18 nucleotides instead of the standard 20), which have been shown to reduce off-target activity while maintaining on-target editing[75]. Base editors and prime editors represent alternative gene editing technologies that do not rely on double-strand break formation, thereby reducing the risk of off-target insertions, deletions, and large genomic rearrangements[76]. Comprehensive off-target detection methods, including whole-genome sequencing, GUIDE-seq, and CIRCLE-seq, are essential for evaluating the safety profile of CRISPR-Cas9 therapeutics before clinical application[77].

Delivery Systems for CRISPR-Cas9

Delivering CRISPR-Cas9 components to the CNS remains one of the most formidable technical barriers to clinical translation. The blood-brain barrier (BBB) serves as a protective shield that prevents approximately 98% of small molecules and nearly all large molecules, including viral vectors and

nanoparticles, from entering the brain parenchyma[78]. This selective permeability is maintained by tight junctions between endothelial cells, efflux transporters, and limited transcytosis[79]. Consequently, systemic delivery of CRISPR-Cas9 therapeutics results in poor brain penetration and requires extremely high doses, which increase the risk of off-target effects and immune responses in peripheral tissues[80]. Several strategies are being developed to overcome BBB limitations. Direct intracerebral or intrathecal injection bypasses the BBB but is highly invasive, carries risks of infection and inflammation, and achieves limited distribution within the brain[81]. Focused ultrasound combined with microbubble administration can transiently disrupt the BBB in a spatially targeted manner, allowing systemic delivery of CRISPR-Cas9 vectors to specific brain regions[82]. This approach has shown promise in preclinical studies but requires careful optimization to avoid tissue damage and inflammation[83]. Engineering viral vectors with enhanced BBB-crossing capabilities represents another avenue. AAV variants with improved CNS tropism, such as AAV9 and AAV-PHP.eB, have demonstrated increased brain transduction following systemic administration in rodent models[84]. However, these variants show reduced efficiency in larger animals and humans, highlighting species-specific differences in BBB permeability[85]. Receptor-mediated transcytosis, utilizing engineered vectors that bind to receptors expressed on brain endothelial cells, offers a non-invasive approach for BBB crossing[86]. Lipid nanoparticles functionalized with targeting ligands and cell-penetrating peptides are also under investigation for CNS delivery of CRISPR-Cas9 ribonucleoprotein complexes[87].

Immune Responses

The immunogenicity of CRISPR-Cas9 components poses another significant challenge for therapeutic applications. The bacterial-derived Cas9 protein can elicit both innate and adaptive immune responses in mammalian hosts[88]. Studies have revealed that a substantial proportion of the human population has pre-existing adaptive immunity to Cas9 orthologs, particularly Streptococcus pyogenes Cas9 and Staphylococcus aureus Cas9[89,90]. Pre-existing antibodies against Cas9 could neutralize the therapeutic agent, reducing efficacy, or trigger adverse immune reactions. Additionally, the innate immune system can recognize foreign DNA and RNA introduced during CRISPR delivery, activating inflammatory pathways that may lead to the clearance of edited cells or systemic inflammation[91]. Strategies to mitigate immune responses include immunosuppression protocols during treatment, engineering of Cas9 variants with reduced immunogenicity, transient delivery of CRISPR components as ribonucleoprotein complexes rather than DNA-encoded vectors, and screening patients for pre-existing immunity before treatment[92]. The development of Cas9 orthologs from bacterial species with lower seroprevalence in humans also offers promise for reducing adaptive immune responses[93].

Ethical and Regulatory Considerations

The application of CRISPR-Cas9 in treating neurodegenerative diseases raises several ethical and regulatory issues that must be carefully addressed. A primary concern is the distinction between somatic and germline gene editing[94]. Somatic gene editing, which targets non-reproductive cells and therefore does not affect future generations, is generally considered more ethically acceptable and is the focus of current therapeutic development[95]. In contrast, germline editing results in heritable genetic changes that raise profound ethical questions regarding consent, unintended consequences, and the potential for genetic enhancement[96]. The international scientific community has called for a moratorium on clinical applications of heritable human genome editing until appropriate ethical and regulatory frameworks are established[97]. Additional ethical considerations include ensuring equitable access to CRISPR-Cas9 therapies, which are likely to be expensive and initially available only in advanced healthcare settings[98]. The potential for unequal access could exacerbate healthcare disparities and widen the gap between populations with access to advanced genomic medicine and those without[99]. Informed consent is another critical issue, particularly for neurodegenerative disease patients who may have cognitive impairments affecting their decision-making capacity[100]. Long-term monitoring of gene-edited patients is essential to detect delayed adverse effects, but it raises questions about privacy and surveillance duration[101]. Regulatory agencies such as the FDA are developing frameworks for evaluating the safety and efficacy of gene editing therapies as the technology advances[102].

Future Directions

The field of CRISPR-Cas9 gene editing for neurodegenerative diseases is rapidly advancing, with several promising directions for future research and clinical development. Next-generation gene editing technologies, including base editors, prime editors, CRISPR interference, and CRISPR activation systems, offer enhanced precision and expanded capabilities beyond traditional Cas9-mediated double-strand break formation[103]. Base editors can directly convert one DNA base to another without creating double-strand breaks, enabling the correction of point mutations with reduced risk of off-target effects[104]. Prime editors provide even greater versatility by allowing targeted insertions, deletions, and base substitutions without requiring donor DNA templates[105]. Combination therapies integrating CRISPR with other therapeutic modalities such as small molecule drugs, antibody treatments, or stem cell therapies may provide synergistic benefits[106]. For example, CRISPR-edited induced pluripotent

stem cell-derived neurons could be transplanted into patients to replace lost neurons in Parkinson's or Huntington's disease [107]. Advances in machine learning are also improving guide RNA design algorithms, enabling more accurate prediction of on-target efficiency and off-target activity [108]. Clinical trials of CRISPR-based therapies for genetic diseases are already underway, with several showing encouraging results [109,110]. The success of early in vivo CRISPR therapies targeting transthyretin amyloidosis demonstrates the feasibility of gene editing in humans and may pave the way for similar approaches in neurological disorders.

Conclusion

CRISPR-Cas9 gene editing represents a paradigm shift in the approach to treating neurodegenerative diseases, offering the potential to address the genetic root causes of PD, HD, AD, and ALS rather than merely managing symptoms. The precision and versatility of CRISPR-Cas9 enable targeted correction of disease-causing mutations, modulation of gene expression, and exploration of disease mechanisms in unprecedented detail. Preclinical studies have demonstrated proof-of-concept for CRISPR-Cas9 therapies in cellular and animal models of these disorders, with promising results in reducing pathological protein aggregation, improving cellular function, and slowing disease progression. However, significant challenges must be overcome before CRISPR-Cas9 can be safely and effectively applied in clinical settings. Off-target effects, delivery barriers—particularly the blood-brain barrier—immune responses, and ethical considerations all require careful attention and innovative solutions. The development of high-fidelity Cas9 variants, advanced delivery systems, immunomodulatory strategies, and robust regulatory frameworks will be essential for the successful translation of CRISPR-Cas9 therapies from bench to bedside. As the field continues to evolve, interdisciplinary collaboration among molecular biologists, neurologists, bioengineers, ethicists, and policymakers will be crucial for navigating the complex landscape of gene editing therapeutics. With continued research and technological innovation, CRISPR-Cas9 holds the promise of transforming the treatment of neurodegenerative diseases and improving the lives of millions of patients worldwide.

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