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ADAR-mediated RNA editing in CNS disorders: from pathogenic mechanisms to therapeutic opportunities

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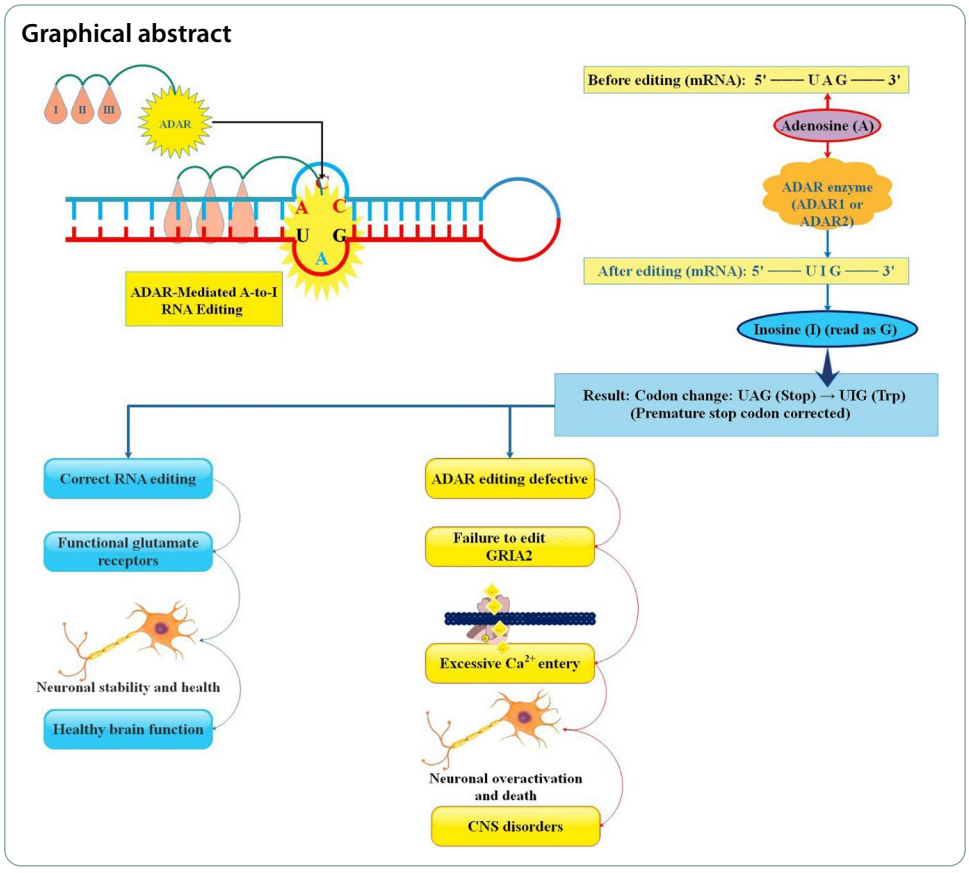
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Abstract

The adenosine deaminases acting on RNA (ADAR) family of enzymes (ADAR1 and ADAR2) catalyze adenosine-to-inosine (A-to-I) RNA editing. This post-transcriptional change is remarkably prevalent in the central nervous system (CNS). ADAR-mediated editing is critical for proper brain development, synaptic plasticity, and immunological homeostasis in the central nervous system (CNS) via recoding neurotransmitter receptors and ion channels. Conversely, a wide range of CNS disorders, such as neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis), neuropsychiatric conditions (schizophrenia, bipolar disorder, and major depression), cerebrovascular diseases, and gliomas, are now linked to dysregulation of ADAR activity, whether through loss-of-function mutations, altered expression, or mislocalization. To address the main question of whether altered RNA editing is a fundamental driver of pathogenesis, a compensatory response, or a context-dependent modulator, this review critically synthesizes existing evidence. The basic processes of ADAR enzymes and their regulation throughout neurodevelopment are first described. Next, we thoroughly assess the unique molecular fingerprints of ADAR dysregulation across several CNS disorders, emphasizing recurring themes such as Alu RNA hypo-editing, induction of innate immunity, and GRIA2 editing, which can cause excitotoxicity. Lastly, we examine new treatment approaches that use or reinstate ADAR activity, such as small-molecule modulators and site-directed RNA editing tools (leveraging endogenous ADAR for programmable editing of RNA [LEAPER], clustered ADAR-recruiting guide RNAs (gRNAs) for effective RNA editing [CLUSTER], and mimicking inverted repeats to recruit ADARs using engineered oligoribonucleotides [MIRROR]). We summarize by reviewing key obstacles to clinical translation, including crossing the blood–brain barrier, the risks of off-target editing, and the challenges of achieving spatiotemporal accuracy. We also list important open topics for further investigation.

Keywords RNA editing, ADAR enzymes, Central nervous system, Neurodegeneration, Therapeutic targets

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Introduction

With the potential for long-term functional restoration via DNA- or RNA-based therapeutics, gene therapy has become a viable alternative to traditional pharmacotherapy for central nervous system (CNS) diseases [1]. Adenosine-to-inosine (A-to-I) editing is one of the most common post-transcriptional RNA modifications in the CNS and is crucial for healthy brain development and function. It is performed by adenosine deaminases acting on RNA (ADAR) [2, 3]. In double-stranded RNA (dsRNA), ADAR1 and ADAR2 convert adenosine to inosine. This mechanism recodes ion channels and neurotransmitter receptors, controls splicing and microRNA (miRNA) targeting, and stops unwanted immune activation by designating endogenous dsRNA as "self" [4–6]. In contrast, ADAR3 may act as a competitive inhibitor in the brain and lacks catalytic activity [4].

The editing of the glutamate receptor subunit GluA2 (also called GluR2) by ADAR2 represents a key paradigm in the area. In the ion channel pore, editing changes a glutamine (Q) codon to an arginine (R) codon, making α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors impermeable to Ca^{2+} and preventing excitotoxicity [5]. A wide range of CNS disorders, including neurodegenerative diseases (Alzheimer's disease [AD], Parkinson's disease [PD], amyotrophic lateral sclerosis [ALS]), neuropsychiatric conditions (schizophrenia, bipolar disorder [BPD]), autoimmune encephalopathy (Aicardi–Goutières syndrome [AGS]), and brain tumors, are increasingly associated with loss of this editing event, or dysregulation of ADAR1-mediated immune surveillance [6, 7]. Notably, primate-specific Alu (a family of short, interspersed, repetitive DNA elements) elements account for more than 99% of editing

sites, in which inverted repeats provide the dsRNA structures required for ADAR binding [7].

This study examines a crucial open question: In many CNS disorders, does altered ADAR-mediated RNA editing function as a major driver of pathogenesis, a compensatory reaction, or a context-dependent modulator (Fig. 1)? First, we provide an overview of the basic processes of ADAR enzymes and their functions in synaptic plasticity and neurodevelopment. The data connecting ADAR dysregulation to certain neurological and neuropsychiatric disorders, as well as CNS malignancies, are then methodically assessed. Lastly, we analyze new treatment approaches that use or restore ADAR activity, such as small-molecule modulators and site-directed RNA editing (SDRE) tools, and we review the main obstacles to clinical translation, including delivery, specificity, and safety.

ADAR enzymes and mechanisms of RNA editing

ADARs catalyze the deamination of adenosine (A) to inosine (I) within dsRNA substrates. Humans encode three ADAR genes: ADAR1 (official symbol *ADAR*), ADAR2 (*ADARB1*), and ADAR3 (*ADARB2*) [16, 17]. ADAR1 and ADAR2 possess well-established catalytic activity, whereas ADAR3, primarily expressed in the brain, lacks deaminase activity, likely due to an inability to homodimerize, and is thought to function as a competitive inhibitor of ADAR1 and ADAR2 [18, 19].

Every ADAR has a modular structure with a C-terminal deaminase domain and at least two N-terminal dsRNA binding domains (dsRBDs). Three dsRBDs and one or two Zα domains, depending on the isoform, are present in ADAR1. These domains bind left-handed nucleic acids and have been implicated in preventing the activation of pathogenic interferon (IFN) via Z-DNA-binding protein 1 [20, 21]. ADAR3 has two dsRBDs and an arginine-rich domain, while ADAR2 has two dsRBDs and no Zα domains [22]. The different substrate specificities of ADAR1 and ADAR2, resulting from a gene duplication event around 700 million years ago [22], are likely due to their distinct domain topologies [22] (Fig. 2).

Regulation and functional consequences

IFN-I, ADAR1 copy number (1q amplification), and small ubiquitin-like modifier-1 modification are some of the variables that control ADAR1 expression and activity. Together, these factors account for around 53% of the variability in expression (25, 26). The molecular consequences of ADAR editing depend on the target region. In coding sequences, A-to-I conversion can alter amino acid sequences, change RNA secondary structure, and modify protein function. In noncoding regions (introns, 5′ untranslated regions [UTRs], and 3′ UTRs), editing affects transcript stability, splicing, miRNA processing, and target recognition. Significantly, via protein–protein interactions with the spliceosome, ADAR1 may also affect splicing irrespective of its catalytic activity [25, 27].

In humans, the majority of ADAR-mediated editing takes place within Alu repetitive sequences, where two inversely oriented Alu elements pair to form dsRNA structures. Despite the high frequency of editing at these sites, recoding events that change protein amino acid sequences are uncommon. In addition to messenger RNAs, ADARs also target noncoding RNAs (ncRNAs), such as precursor transfer RNAs (tRNAs), primary miRNAs (pri-miRNAs), and long ncRNAs (lncRNAs). Approximately 10–20% of

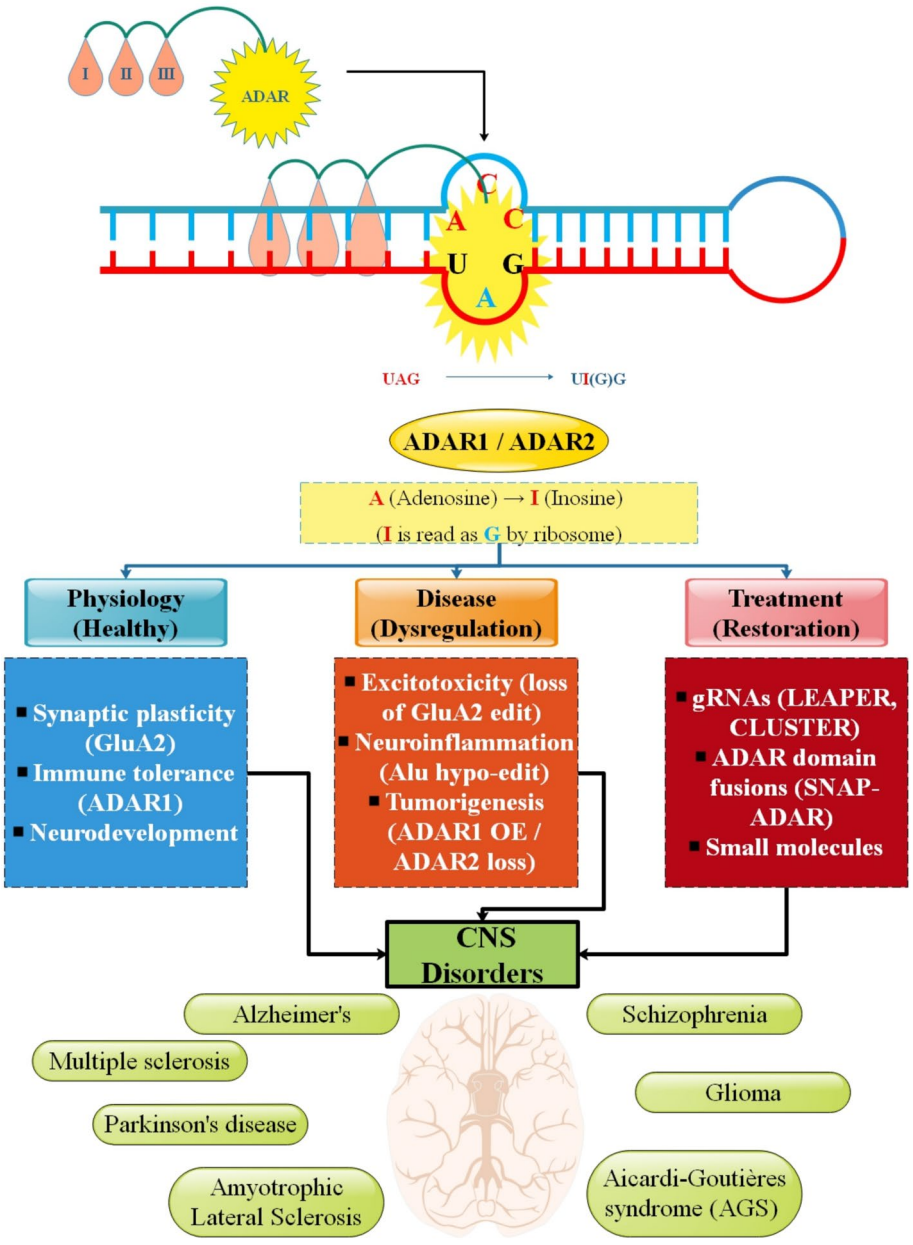


Fig. 1 An overview of CNS health, illness, and treatment using ADAR-mediated A-to-I RNA editing. Within dsRNA, ADAR1 and ADAR2 catalyze the conversion of adenosine (A) to inosine (I). The translational machinery then reads inosine as guanosine (G), thereby altering the potential for protein coding [8, 9]. This editing controls neurodevelopment, immunological tolerance (ADAR1-mediated Alu RNA editing), and synaptic plasticity in the healthy CNS (physiology) [10]. In contrast, deregulation of ADAR activity (disease) causes cancer due to ADAR1 overexpression or ADAR2 loss, excitotoxicity via loss of GluA2 editing, and neuroinflammation through Alu RNA hypo-editing [11, 12]. New therapeutic approaches (treatment) use small chemical modulators or synthetic guide RNAs (gRNAs) (leveraging endogenous ADAR for programmable editing of RNA [LEAPER], clustered ADAR-recruiting gRNAs for effective RNA editing [CLUSTER], ADAR domain fusions, SNAP-ADAR) to restore editing function [13]. Numerous CNS conditions, including AD, PD, ALS, multiple sclerosis (MS), schizophrenia, glioma, and AGS, have been linked to dysregulated ADAR editing [6, 14, 15]. This figure was created using EdrawMax software

pri-miRNAs are subject to A-to-I editing, which can influence their maturation process and modify their ability to recognize target messenger RNAs. In some cases, a single editing event within the seed region of a miRNA can substantially reshape its target gene repertoire [28].

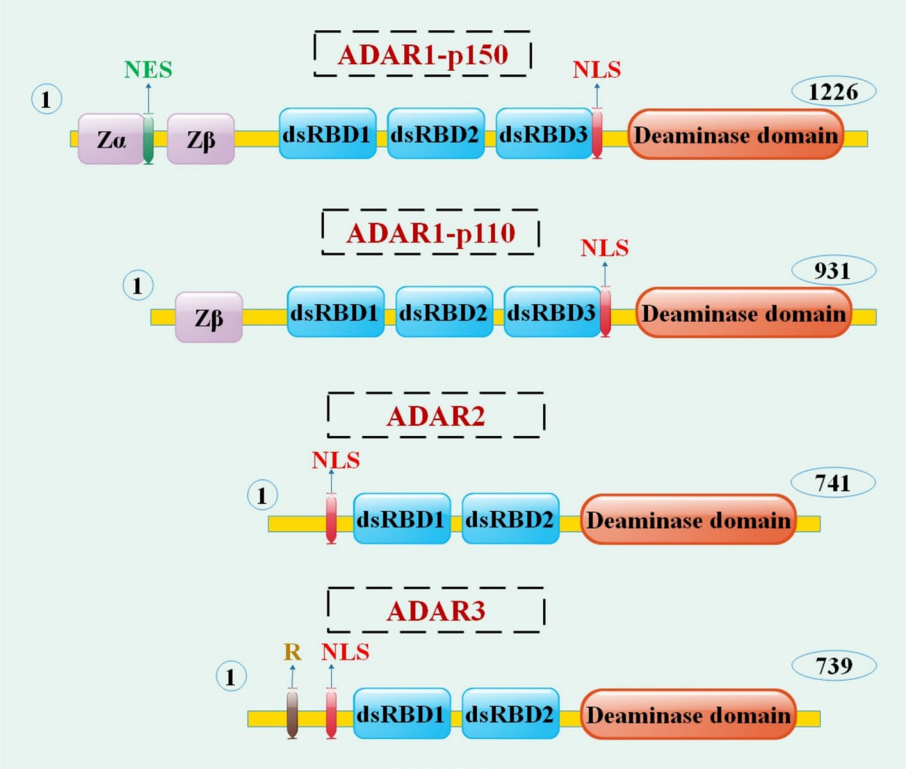


Fig. 2 Human ADARs share a common structural framework, featuring a C-terminal deaminase domain (orange) and variable numbers of dsRBDs (blue). ADAR3 is distinguished by an arginine–glycine (RG)-rich region at its N-terminus (brown). The *ADAR1* gene produces two major protein isoforms: the constitutively expressed nuclear ADAR1 p110 and the IFN-inducible cytoplasmic ADAR1 p150. Both isoforms contain a Zβ domain (ZBD; purple) and a nuclear localization sequence (NLS; red). The longer ADAR1 p150 isoform additionally possesses a Zα DNA-binding domain and a nuclear export sequence (NES; green) at its N-terminus [23, 24]. This figure was created using EdrawMax software

Substrate selectivity and dimerization

There is still much to learn about the processes controlling ADAR substrate selection. It appears that stable binding is necessary for effective deamination, since ADAR2 binds to its modified target sites steadily but only transiently at nonselective sites [29, 30]. A long-standing dispute over ADAR dimerization has been settled by structural and biochemical research: ADAR2 forms asymmetric dimers on dsRNA, in which one deaminase domain contacts the back of the other to position its active site for editing [9, 29, 31]. Catalytic activity depends on this dimerization process.

Structural basis of editing

Structural studies have shown that ADAR's intercalating loop accesses the target adenosine from the minor groove side, triggering substantial conformational changes within the RNA duplex [30, 32, 33]. The nucleotide immediately 5′ to the editing site (the –1 base) becomes unstacked, and its ribose conformation shifts from the typical C3′-endo found in A-form RNA to a C2′-endo pucker characteristic of B-form DNA. These structural rearrangements widen the minor groove and introduce a kink in the non-edited strand. This requirement explains why ADARs cannot act on deoxyadenosines within B-form DNA duplexes: The minor groove is too narrow to accommodate the base-flipping loop.

However, ADARs can deaminate 2′-deoxyadenosines in DNA/RNA hybrid duplexes, as these hybrids adopt an A-like helical conformation [30] (Fig. 3).

ADARs in neurodevelopment and synaptic plasticity

During brain development, ADAR-mediated RNA editing is tightly regulated and plays an indispensable role in CNS maturation and synaptic transmission. Both coding and ncRNAs are targeted for editing, influencing splicing patterns, miRNA binding, and ultimately protein output. While recoding events are uncommon, those that occur at evolutionarily conserved sites in genes such as *GRIA2*, *HTR2C*, *NOVA1*, and *GABRA3* are essential for proper nervous system function [34, 35]. AD, autism spectrum disorder (ASD), ALS, schizophrenia, and BPD have all been associated with reduced A-to-I editing, often accompanied by matching reductions in ADAR2 expression (35) (Tables 1 and 2).

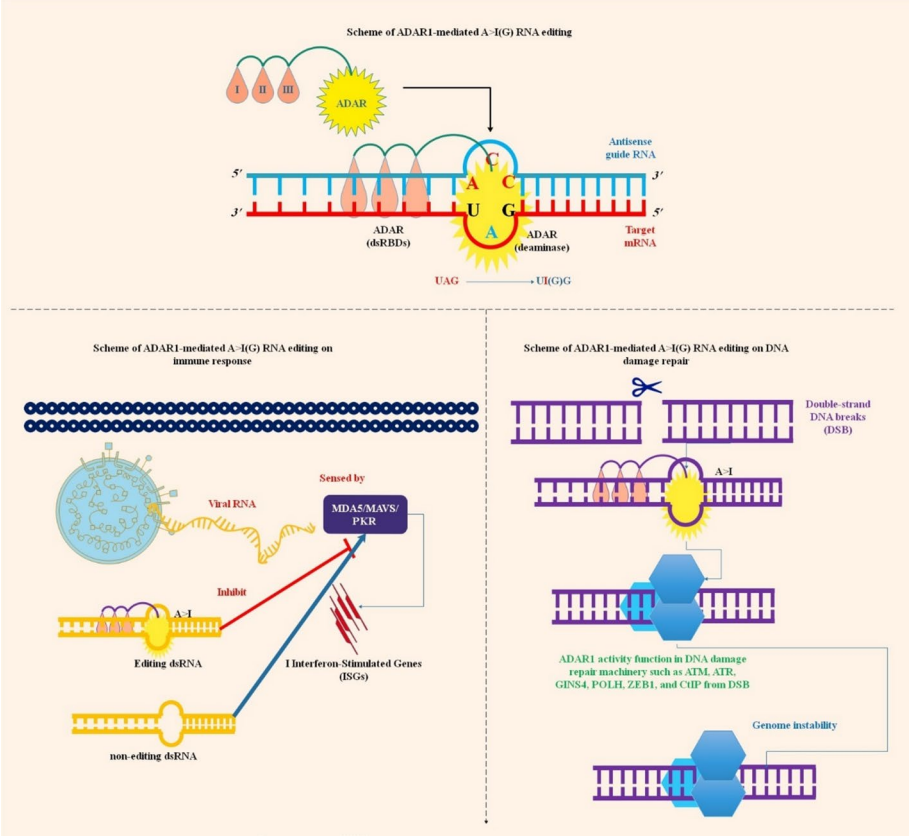


Fig. 3 An illustration of the functional implications of A-to-I (G) RNA editing mediated by ADAR1. The core editing process, which produces a dsRNA substrate by base-pairing an antisense gRNA with the target mRNA, is seen in the top panel. After binding this duplex, ADAR1 changes adenosine (A) into inosine (I), which the cellular machinery then recognizes as guanosine (G). The center panel illustrates the function of ADAR1 in immune regulation: Although unedited dsRNA is detected by pattern recognition receptors, including melanoma differentiation-associated protein 5 (MDA5), mitochondrial antiviral signaling protein (MAVS), and protein kinase R (PKR), which activate IFN-stimulated genes (ISGs), edited dsRNA is protected from identification. ADAR1's role in DNA damage repair is seen in the bottom panel. Through elements such as ataxia telangiectasia mutated (ATM), ATM and Rad3-related, GINS4, POLH, ZEB1, and CtIP, ADAR1 activity helps repair double-strand DNA breaks, thereby reducing genomic instability [25]. This figure was created using EdrawMax software

Table 1 Summary of key ADAR substrates in the CNS, their editing sites, functional consequences, and associated disorders

Substrate	Editing site	ADAR enzyme	Functional consequence	Disrupted editing phenotype	Ref
GRIA2 (GluA2)	Q/R (codon 607)	ADAR2	Reduces Ca^{2+} permeability of AMPA receptors; prevents excitotoxicity	Increased Ca^{2+} influx via AMPA receptors induces excitotoxicity, heightens seizure vulnerability, and expedites neuronal degeneration	[36, 37]
HTR2C (5-HT2C receptor)	Multiple sites (A, B, C, D, E)	ADAR1, ADAR2	Modifies G-protein coupling, agonist affinity, and serotonin signaling	Disruption of normal serotonin signaling has been linked to depression, increased suicide risk, and post-traumatic stress disorder (PTSD)	[38]
GRIA3 (GluA3)	Q/R (rare)	ADAR2	Modulates AMPA receptor characteristics	Impaired synaptic transmission	[39]
GRIK2 (GluK2)	I/V (intron/exon boundary)	ADAR2	Modifies kainate receptor Ca^{2+} permeability	Mood disorders, BPD	[40]
KCNA1 (Kv1.1)	I/V	ADAR2	Regulates potassium channel inactivation	Altered neuronal excitability	[41]
GABRA3	I/M (p.I343M)	ADAR1, ADAR2	Influences GABA-A receptor activity	Decreased ADAR editing in glioma enhances metastatic capability, characterized by enhanced motility and tissue penetration	[42]
BLCAP	Multiple sites	ADAR2	Regulates tumor suppressors	Increased cell proliferation via Akt/mTOR or STAT3	[43]
NOVA1	Multiple sites	ADAR1, ADAR2	Modulates alternative splicing in neurons	Impaired neuronal development	[34]

Table 2 Summary of the phenotypes of ADAR knockout and knockdown models, highlighting the distinct roles of ADAR1 and ADAR2 in development versus synaptic function

Model system	Consequence of ADAR1 deficiency	Consequence of ADAR2 deficiency	Ref
Global knockout (mouse)	Embryonic lethal at E11.5–E13.5 due to IFN-driven apoptosis	Perinatal lethal (within 0–21 days after birth), accompanied by severe epilepsy	[36, 44]
Conditional CNS knockout	Profound neurodevelopmental abnormalities, including microcephaly	Epileptic seizures and motor function deficits	[36, 41, 44]
Rescue with edited GluA2	Not applicable	Restores viability and prevents epilepsy, demonstrating that GluA2 editing is essential for survival	[36, 44]
Drosophila ADAR mutant	N/A (flies possess a single *ADAR* gene)	Elevated sleep pressure, abnormalities in synaptic vesicles, and compromised neurotransmission	[45, 46]
Heterozygous ($ADAR2^{+/-}$)	Not reported	Reduced R/G editing of AMPA receptors, hyperactivity, and antidepressant-like behavioral effects	[47]
Human mutations	AGS is characterized by severe neuroinflammation	Developmental and epileptic encephalopathy (DEE) with microcephaly and intellectual disability	[48–50]

AMPA receptor editing: a paradigm for neurodevelopmental regulation

The most extensively characterized editing event in the CNS occurs at the Q/R site of the *GRIA2* transcript, where ADAR2 converts a glutamine (Q) codon to arginine (R) within the ion channel pore of the AMPA receptor (Fig. 4). This single amino acid substitution reduces Ca^{2+} permeability by introducing a positively charged residue, thereby protecting neurons from excitotoxic cell death. In the human brain, nearly 100% of *GRIA2* mRNA is edited at this site, making GluA2-containing AMPA receptors

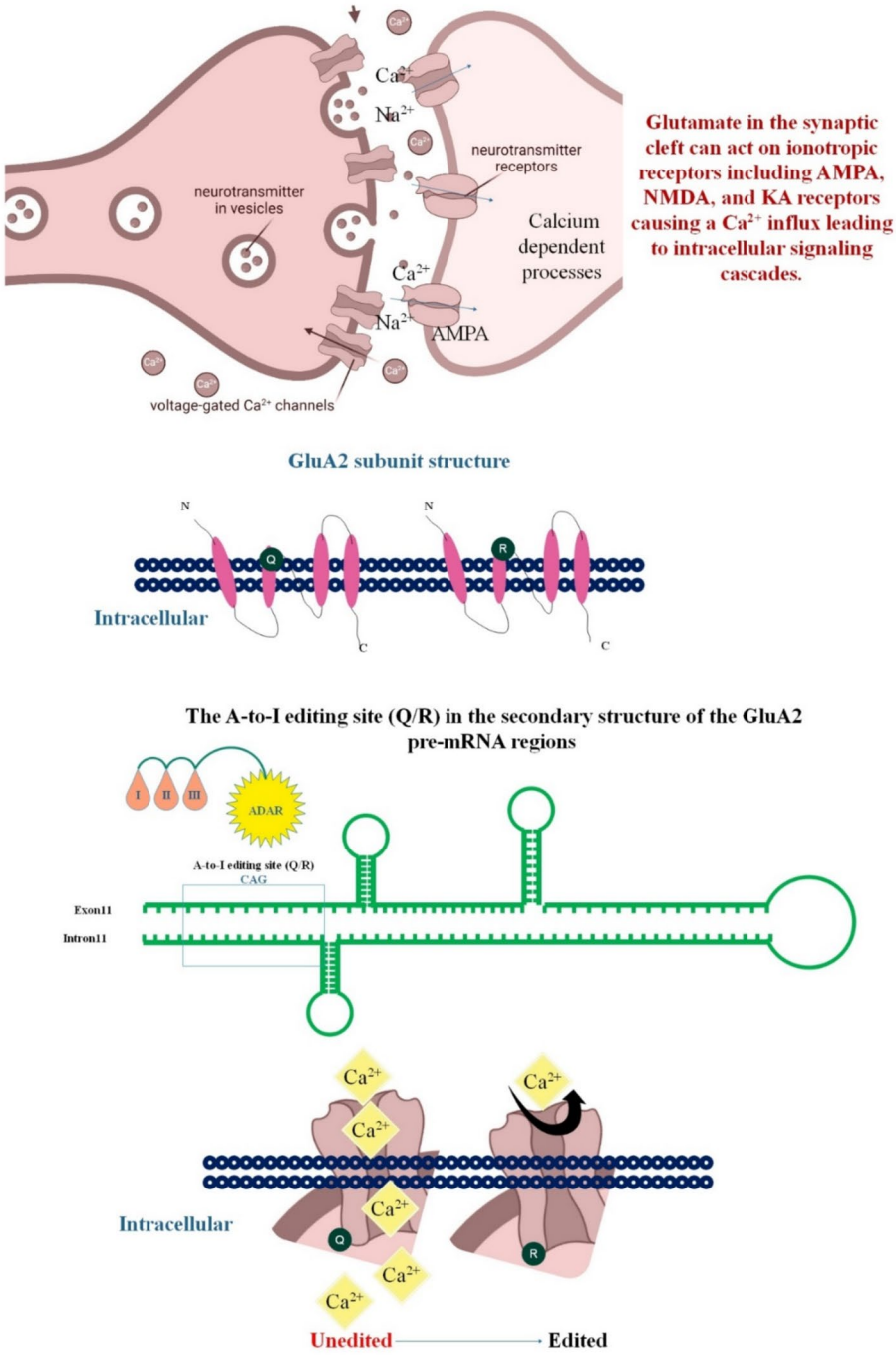


Fig. 4 Within the suggested second membrane domain, the AMPA receptor site's Ca^{2+} permeability is controlled by the Q/R RNA editing site. Ahead of the membrane's fourth domain are the R/G and flip/flop sites, which regulate receptor desensitization. While all four of these genes encode glutamine, GluA2's protein sequence varies from the others by one codon—Arg. An RNA editing-induced amino acid alteration in GluA2's pre-mRNA introduces the Arg post-transcriptionally [51]. This figure was created using EdrawMax software

Ca^{2+}-impermeable [36, 37]. Mice lacking ADAR2 die prematurely from epilepsy, but this phenotype is completely rescued by introducing an edited *Gria2* transgene, demonstrating that the Q/R editing event is ADAR2's critical survival function [36, 37, 44].

In addition to the Q/R site, ADARs can modulate AMPA receptor desensitization via R/G editing sites and flip/flop alternative splicing (Fig. 4). The timing of these editing

processes is meticulously regulated: Editing efficiency increases both geographically and temporally as the brain develops, with neurons exhibiting higher editing levels than non-neuronal cells [3, 41].

Although research by Higuchi et al. [36, 37] showed that GRIA2 Q/R editing is a crucial survival function of ADAR2, several questions remain. First, it is unclear whether additional ADAR2 substrates support higher-order brain function, as the modified Gria2 rescue model has not been thoroughly phenotyped for cognitive or behavioral abnormalities. Second, there is still no molecular explanation for the finding that neurons have greater editing levels than non-neuronal cells [3, 41]. Future research should use single-cell editing profiling to identify cell-type-specific regulators and conditional, temporally controlled ADAR2 knockouts, such as CamKII-Cre-ER, to determine when editing becomes crucial during development. Third, knock-in mice missing these locations are required because the functional importance of flip/flop splicing and R/G editing has not been examined in vivo. Lastly, using ADAR-recruiting technologies (LEAPER, CLUSTER) in ADAR2-deficient animal models or patient-derived neurons to restore GRIA2 editing in sporadic ALS and AD, where ADAR2 expression is decreased, is necessary to translate our results to human illness [35].

ADAR1, immune regulation, and neurodevelopment

The primary function of ADAR1 in the CNS is immunological tolerance. ADAR1 prevents cytosolic sensors such as MDA5 from recognizing endogenous dsRNA, thereby preventing unwanted IFN activation. Maternal immune activation (MIA) models show that this function is crucial during brain development: Poly(I:C)-treated pregnant mice produce offspring with dysregulated gene circuits involved in brain development and temporarily reduced RNA editing, but behavioral deficits last into adulthood [52, 53]. Studies demonstrating that concomitant MDA5 deletion rescues the fatal phenotype of ADAR1 knockout, suggesting that unregulated innate immune sensing causes the disease, highlight the significance of ADAR1's editing role [53]. AGS, a severe autoinflammatory encephalopathy in humans marked by brain inflammation, cognitive impairment, and motor abnormalities, is caused by loss-of-function mutations in *ADAR1* [6].

Although the importance of ADAR1-mediated immunological tolerance in brain development is accurately identified in this section, significant gaps remain. First, the MIA model demonstrates temporary editing alterations but long-lasting behavioral abnormalities [52, 53]; longitudinal editing profiles should be used in future research to determine when therapeutic intervention could improve results. Second, conditional knockouts are required because it is uncertain whether cell types such as microglia, neurons, or astrocytes cause AGS disease. Third, examining postmortem fetal tissue from maternal infection cases would address the question of whether MIA-induced editing alterations occur in humans. Lastly, investigating RNase L inhibitors, such as derivatives of ellagic acid (EA) or ADAR1-independent IFN blocking in patient-derived cells, may be a therapeutic approach for AGS.

Synaptic plasticity and homeostatic regulation

Homeostatic synaptic plasticity relies on activity-dependent regulation of ADAR editing. When neuronal activity is chronically suppressed, ADAR2 levels in the nucleus decrease, resulting in reduced GRIA2 editing and increased surface expression of Ca^{2+}-permeable

AMPA receptors, a process known as homeostatic upscaling. In cultured neurons, this upscaling is blocked by either ADAR2 overexpression or CRISPR–Cas13-mediated direct editing of GRIA2 transcripts [10]. Consistent with these findings, dark-reared mice show reduced GluA2 Q/R editing in the primary visual cortex (V1), and viral overexpression of ADAR2 in V1 prevents homeostatic plasticity [10].

The function of ADAR in synaptic function has been further clarified by research conducted in *Drosophila*. Loss of Adar causes *N*-methyl-D-aspartate receptor overactivation, increased expression of vesicular glutamate transporters, and larger synaptic vesicle pools, thereby disrupting synaptic depression and increasing sleep pressure [45, 46, 54]. *ADAR* mutants show increased quantal size, decreased neurotransmitter release probability, and altered calcium dependence of synaptic transmission at the neuromuscular junction, along with compensatory modifications in muscle membrane characteristics [46]. All of these results point to the need for ADAR-mediated editing to maintain synaptic homeostasis across all species.

Although ADAR2-mediated GRIA2 editing is accurately identified in this section as crucial for homeostatic plasticity, important gaps remain. Future research should identify upstream kinases or ubiquitin ligases, as the activity-dependent pathway regulating nuclear ADAR2 levels remains unclear. Double-rescue studies that express solely modified GRIA2 in ADAR2-deficient neurons are necessary to examine whether additional ADAR substrates contribute to scaling beyond GRIA2. Furthermore, conditional ADAR2 knockouts with electrophysiological and sleep monitoring are needed to validate the remarkable *Drosophila* phenotypes (altered vesicle pools, release probability, and sleep pressure) in humans. Lastly, assessing GRIA2 editing levels in postmortem brain tissue from individuals with autism, epilepsy, or sleep problems is necessary for clinical translation [45, 46, 54].

Dysregulated RNA editing in CNS disorders

RNA regulatory networks are essential for brain development, function, and susceptibility to neurological disease. Disruption of these networks, including RNA editing, ncRNAs, and epigenetic modifications, contributes to the pathogenesis of major neurodegenerative disorders such as AD, PD, Huntington's disease, and ALS [55, 56]. A-to-I editing patterns are very cell-type-specific: 189,229 cell-type-associated editing sites have been found in the human prefrontal cortex, where neurons show greater levels of selective and hyper-editing than oligodendrocytes. Additionally, a comprehensive genomic map connecting cell-type-specific editing to regulatory effects has been created by mapping 661,791 *cis*-editing quantitative trait loci (edQTLs) across 13 brain regions [57].

Dysregulated RNA editing has been increasingly linked to both viral neuropathology and disorders involving repeat expansions. For Zika virus infection, one hypothesis posits that neurodevelopmental abnormalities arise from disrupted ADAR-mediated editing, implying that the host's innate immune response may inadvertently fuel pathogenesis [58]. In cytosine–adenine–guanine (CAG) repeat expansion disorders such as Huntington's disease, midbrain organoid studies revealed no global changes in editing levels in most cultures. Nevertheless, organoids harboring the longest huntingtin CAG repeats displayed substantial reductions in editing of specific transcripts, including the

lncRNA PWAR5. Despite these observations, the proposed mechanism, that repeat RNAs directly interfere with ADAR function, remains unconfirmed [59].

Single-base mutations in the CNS may be corrected thanks to recent medical developments. The *MEF2C* mutation (*c.104T > C, p.L35P*) linked to ASD in mice was effectively fixed by researchers using an apolipoprotein B mRNA-editing enzyme (AeCBE)-based base editor administered by adeno-associated virus. In addition to improving social impairments, hyperactivity, and repetitive behaviors, this therapy restored MEF2C protein levels, providing a viable therapeutic approach for brain mutations involving single-base substitutions [60].

ADAR1 has become recognized as a key mediator of CNS injury and repair, especially in ischemic stroke. After a stroke, ADAR1 drives reactive oxygen species production and the proliferation of activated astrocytes, initiating inflammatory pathways that worsen neuronal death. Beyond its role in injury, ADAR1 also governs RNA editing that shapes gene expression during brain development and maturation. Thus, modulating ADAR1 activity may uncover new therapeutic targets for both neurodevelopmental disorders and ischemic stroke [6]. The subsequent subsections detail the strong associations between ADAR1 and various CNS diseases.

Alzheimer's disease

In AD, ADAR dysfunction is both cell-type- and region-specific, manifesting distinctly in neurons, vasculature, and glial cells. Transcriptome-wide profiling of 1865 brain samples from 1074 individuals across nine regions identified 58,761 novel RNA editing events, a subset of which were validated at the protein level. Among these, editing events linked to AD dementia, neuropathological severity, and longitudinal cognitive decline mapped to genes including *SYT11*, *MCUR1*, *SOD2*, *ORAI2*, *HSDL2*, *PFKP*, and *GPRC5B* [61]. Hippocampal ADAR2 is downregulated in the J20 AD mouse model, but GluA3 and ADAR1 p110 are increased. Significant correlations among these editing enzyme modifications, AMPA receptor subunit changes, and ADAR stability-regulating proteins (PIN1, WWP2, FXR1P, and CREB1) are revealed by regression analyses, indicating that dysregulation of RNA editing-related proteins contributes to synaptic dysfunction and AD progression [39].

Patients with AD show a small but significant decrease in A-to-I editing, particularly in the hippocampus and hippocampal vasculature, whereas cortical Alu RNA editing remains unaltered. This lack of regional editing leads to a buildup of unedited Alu RNAs, which are potent activators of innate immunity that engage the IFN and NF-κB pathways. However, weak immune activators, or modified Alu RNAs, are more common in healthy controls. These results suggest that local innate immune activation is triggered by loss of Alu RNA editing in the hippocampus vasculature [62]. Extracellular vesicles (EVs) provide a potential route for the spread of this pathology. In AD, cortical EVs exhibit significantly reduced Alu A-to-I editing, with editing patterns resembling those of hippocampal vasculature rather than the whole cortex. This observation suggests that unedited Alu RNAs originating in the hippocampal vasculature are transported to the cortex via EVs, where they promote innate immunity and contribute to disease progression [63].

Finally, age-related declines in ADAR expression and A-to-I editing are observed across multiple systems: Aged mouse astrocytes, aged human astrocytes, and brains of

patients with AD all show reduced ADAR levels compared with younger or healthy controls. In primary human astrocytes, pharmacological or small interfering RNA (siRNA)-mediated ADAR inhibition leads to dsRNA accumulation, increased PKR levels, and elevated proinflammatory cytokines (IL-6) and ICAM-1. Together, these findings indicate that ADAR plays a significant role in regulating neuroinflammation during aging and neurodegeneration [64].

Thousands of hitherto unidentified RNA editing events have been identified in AD brains through large-scale transcriptome analyses, and reduced editing of Alu repeats in the hippocampus is a major factor in innate immune activation via NF-κB and IFN signaling pathways [61, 62]. The J20 mouse model has a similar inflammatory profile, with altered AMPA receptor subunits and dysregulation of proteins that regulate ADAR stability, along with decreased ADAR2 and increased ADAR1 expression [39]. Unedited Alu RNAs that originate in the hippocampal vasculature are carried by EVs isolated from AD cortex, suggesting a route for spreading neuroinflammation beyond the hippocampus [63]. Because ADAR inhibition in astrocytes leads to dsRNA accumulation, PKR activation, and increased proinflammatory cytokine levels, age-related reductions in ADAR expression exacerbate neuroinflammation [64]. Future research should: [1] determine whether restoring Alu RNA editing in the hippocampus (via ADAR-recruiting gRNAs) can rescue cognitive deficits and reduce neuroinflammation in AD mouse models; [2] use conditional knockouts to examine the cell-type-specific contributions of neuronal versus astrocytic ADAR1/ADAR2 to AD pathogenesis; [3] track fluorescently labeled edited versus unedited Alu RNAs in vivo to verify the EV-mediated spread hypothesis; and [4] investigate whether pharmacological ADAR activators can reverse age-related editing declines and postpone the onset of AD.

Amyotrophic lateral sclerosis (ALS)

RNA editing deficits in sporadic ALS

Failure of ADAR2-mediated RNA editing at the Q/R site of the *GRIA2* (GluA2) mRNA is a major mechanism underlying motor neuron loss in ALS. Single-neuron examination of patients with sporadic ALS showed that although control motor neurons had 100% editing efficiency, ALS motor neurons had editing efficiencies ranging from 0% to 100%, with 44.56% of neurons demonstrating insufficient editing. The same patients' cerebellar Purkinje cells, however, maintain > 99% editing, indicating that GRIA2 underediting is disease- and region-specific. Restoring ADAR2 activity may be a targeted therapeutic approach since this editing defect directly causes Ca^{2+}-permeable AMPA receptors and excitotoxic motor neuron death [65].

Molecular subtyping reveals editing changes in ALS-Ox

A molecular subtype of ALS, known as ALS-Ox, has been identified through integrative RNA editing profiling and is characterized by markedly decreased RNA editing in the frontal brain. Genes involved in the glutamatergic and synaptic pathways had higher levels of differentially altered transcripts. Importantly, editing modifications are associated with alterations in the expression of *GRIA2*, *GRIA3*, and *CACNA1C* (which encodes a postsynaptic L-type calcium channel pore), as well as recoding at the Q621R site in *GRIK2*. These results show that RNA editing modifies glutamatergic synaptic transcripts in a molecular subtype of ALS by controlling gene expression and recoding [66].

ADAR2 mislocalization in C9orf72-mediated ALS/frontotemporal dementia (FTD)

The most common genetic driver of ALS and FTD is a GGGGCC hexanucleotide repeat expansion (HRE) within the *C9orf72* gene. In postmortem brain tissue from C9orf72 ALS/FTD, HRE-expressing mice, and patient-derived induced pluripotent stem cell (iPSC) motor neurons, ADAR2 is consistently mislocalized from its normal nuclear compartment to the cytoplasm. Consequently, widespread disruption of A-to-I editing occurs at 408,580 sites, affecting key pathways, including EIF2 signaling and the integrated stress response. These findings point to ADAR2 mislocalization as a driver of aberrant RNA processing, thereby impairing protein translation and cellular stress responses in C9orf72-mediated disease [67].

Significant limitations remain, despite compelling evidence linking ALS etiology to GRIA2 underediting [65], decreased editing of glutamatergic transcripts in the frontal cortex [66], and ADAR2 mislocalization [67]. Since no adult rescue experiment has been carried out, it is uncertain whether decreased GRIA2 editing actually causes motor neuron death or just coincides with neuronal stress. It remains unknown what causes ADAR2 mislocalization in ALS associated with C9orf72 and ADAR2 deletion in sporadic ALS. Owing to the modest sample sizes, validation in larger independent cohorts is necessary. Since no research has examined whether AAV-delivered ADAR2 or ADAR-recruiting gRNAs can enhance survival in adult ALS mice, restore editing, or preserve motor neurons, therapeutic applications are likewise premature. Future research must concentrate on adult rescue studies, the discovery of ADAR2 upstream regulators, and the functional confirmation of editing modifications utilizing electrophysiological tests on patient-derived iPSC neurons.

Parkinson's disease

Editing sites linked to PD risk and cognitive decline

Genetic risk variants may increase PD susceptibility through A-to-I editing. Studies have identified 17 putative causative editing sites for PD, located in genes including *NCOR1*, *KANSL1*, and *BST1* [68]. Additionally, 57 editing sites show long-term associations with cognitive deterioration in patients with PD, suggesting that dynamic editing changes are linked to disease progression [68].

Widespread editing changes and miRNA regulation

In 372 patients with PD, 9897 A-to-I editing events were detected across 6286 genes. Of these, 72 editing events modify miRNA binding sites, potentially influencing host gene regulation via three mechanisms: (1) editing within miRNA seed regions alters target specificity; (2) the formation of new binding sites redirects miRNAs from alternative targets; and (3) the elimination of existing sites liberates genes from miRNA repression. Eight editing events were identified that modified the expression of 1146 genes via miRNA competition, while a single seed-area editing event (miR-4477b) impaired the regulation of four genes. Three editing events in *EIF2AK2*, *APOL6*, and the miR-4477b seed area have been suggested as biomarkers for PD [69].

Reduced editing in PD brains

PD affects the prefrontal cortex's Brodmann area 9 (BA9). This area of the brain's frontal lobe is crucial for memory and motor and cognitive processes. In patients with PD,

BA9 induces the formation of Lewy bodies and exhibits essential alterations in the transcriptome and proteome, which are linked to metallothioneins, protein-folding processes, and mitochondrial pathways [70]. Analysis of BA9 from PD prefrontal cortex revealed overall reduced A-to-I editing levels compared with healthy controls, along with decreased *ADAR* gene expression. Using REDItools to repurpose RNA sequencing (RNA-seq) data, researchers identified PD-specific editing sites, suggesting that altered mRNA modification patterns contribute to PD pathophysiology [70].

Nonsense-mediated decay (NMD) involvement

Transcriptome analysis of 317 samples from the Parkinson's Project Markers Initiative (including prodromal patients, patients with PD, and healthy controls) showed that the groups differed in high-impact edits, editing index, and ADAR expression, especially when editing was associated with NMD. ADAR editing may affect PD etiology by regulating NMD, as shown by the enrichment of NMD pathways among differentially expressed genes [71].

Astrocytic ADAR1 and neuroinflammation

Exposure of human iPSC-derived astrocytes to oligomeric alpha-synuclein triggers activation of the IFN pathway, which in turn upregulates ADAR1 and promotes isoform switching. Consequently, astrocytes adopt a reactive state characterized by increased A-to-I editing and inflammatory signaling, leading to neuronal damage and loss of protective functions. The presence of elevated ADAR1-mediated editing in postmortem PD brains further supports a role for dysregulated astrocytic ADAR1 in driving neuroinflammation in PD [72].

Peripheral biomarkers and nuclear inclusions

An ADARB1-centered module linked to glutamate and phenethylamine, including 109 miRNAs and LINC02960, was identified through blood-based transcriptomic and metabolic profiling. The synergistic interactions of ncRNAs in the blood of patients with AD and PD are highlighted in this module [73]. Furthermore, objective biochemical examination of the brains of patients with PD and dementia with Lewy bodies identified nuclear inclusions that included A-to-I altered mRNAs and NONO and SFPQ proteins. A self-perpetuating pathogenic cycle is created when these inclusions decrease ADAR3 expression, which increases editing of mitochondrial, synaptic, and Alu-repeat transcripts [74] (Fig. 5).

A recent study has identified numerous ways in which RNA editing can go wrong in PD. In addition to specific editing alterations associated with genetic risk factors and cognitive loss, brain tissue from patients with PD generally exhibits decreased A-to-I editing [68, 70]. The way miRNAs control their target genes is similarly disrupted by widespread editing changes [69], and NMD pathways are also implicated [71]. Alpha-synuclein exposure induces ADAR1 overexpression in astrocytes, leading to inflammation and damage to surrounding neurons [72]. A positive feedback loop of editing dysregulation is also driven by aberrant nuclear aggregates containing SFPQ and NONO proteins [74]. In practice, blood-based markers linked to ADARB1 may also serve as future biomarkers for PD [73].

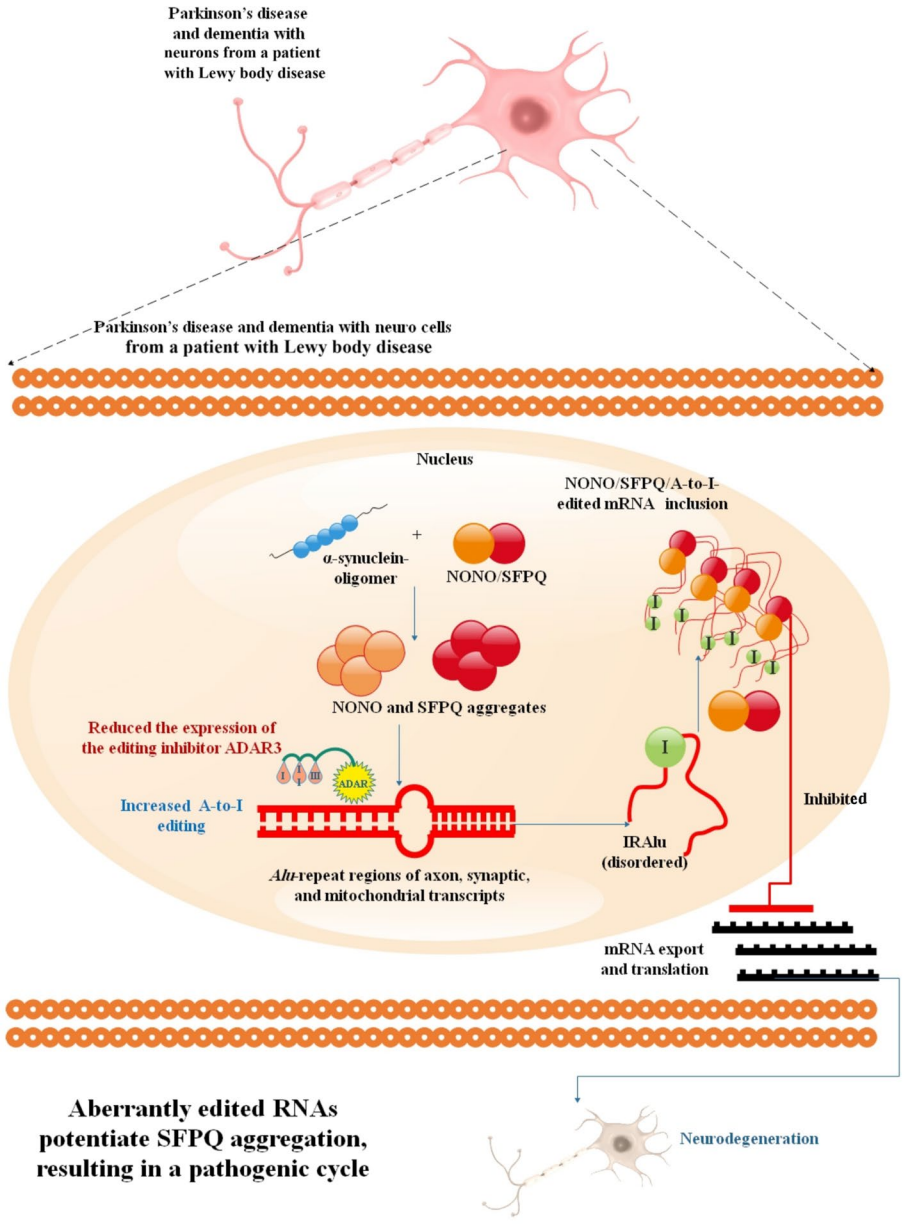


Fig. 5 ADARs primarily target axon and synaptic transcripts, and RNA editing is crucial in human brain development. Changes observed in the brains and blood of patients suggest that A-to-I RNA editing contributes to PD pathogenesis. Researchers isolated and described the functional effects of nuclear inclusions of NONO and SFPQ and altered mRNA [74]. This figure was created using EdrawMax software

Critical limitations include: [1] unproven causality, as editing alterations may be a consequence of neurodegeneration; (2) the majority of studies are observational with limited sample sizes; (3) the mechanisms connecting alpha-synuclein to the upregulation of ADAR1 remain unidentified; and (4) there is a deficiency in functional validation of editing events, including EIF2AK2 and APOL6.

Future research should: (1) evaluate whether the restoration of specific editing events, such as through ADAR-recruiting gRNAs, can rescue dopaminergic neurons in PD models; (2) elucidate upstream signals that connect alpha-synuclein to the induction of ADAR1; (3) authenticate blood-based editing biomarkers in prospective cohorts; and

(4) ascertain whether NONO/SFPQ inclusions are a cause or a consequence of editing dysregulation.

Multiple sclerosis (MS)

Relapsing–remitting MS is associated with elevated IFN responses due to increased levels of endogenous Alu double-stranded RNA. Patients with MS exhibit a generalized reduction in A-to-I editing of Alu RNAs, leading to strong activation of the dsRNA sensors retinoic acid-inducible gene I (RIG-I) and Toll-like receptor 3 (TLR-3), which in turn trigger both IFN and NF-κB transcriptional responses. Notably, even minor editing of highly active Alu elements abolishes their ability to initiate these responses, suggesting that A-to-I editing serves as a critical defense against autoimmune disorders such as MS [75].

Although IFN-β is a first-line treatment for MS, up to 50% of patients fail to respond clinically. In 167 patients with relapsing–remitting MS, elevated ADAR expression and the presence of the A allele at the rs2229857 single-nucleotide variant were associated with poor response to IFN-β. These findings suggest that measuring ADAR transcript levels and genotyping rs2229857 may help predict patient responses before initiating therapy, though further research is needed to validate ADAR as a prognostic biomarker [76].

In the experimental autoimmune encephalomyelitis (EAE) mouse model of MS, RNA editing activity mediated by both ADAR and apolipoprotein B mRNA editing enzyme (APOBEC) deaminases declines sharply as the disease progresses, potentially disrupting the synthesis of proteins essential for normal brain function. APOBEC-1 knockout mice developed significantly more severe EAE than wild-type controls, suggesting that epitranscriptomic regulatory mechanisms contribute to EAE pathophysiology. These observations may also apply to MS and other neurodegenerative conditions [77].

Recent research indicates that MS is associated with diminished Alu RNA editing, leading to aberrant activation of IFN and NF-κB [75]. ADAR expression and the rs2229857 variation may serve as predictors of IFN-β response, but confirmation is required [76]. EAE models demonstrate that ADAR and APOBEC-mediated editing is reduced throughout the illness, with APOBEC-1 knockdown intensifying severity [77].

Contemporary understanding has four principal limitations. The mechanism responsible for Alu RNA accumulation in MS remains unidentified. The potential of ADAR as a biomarker for treatment response has yet to be proven in prospective studies. The direction of causality between editing changes and neuroinflammation has not been established. The distinct roles of ADAR and APOBEC enzymes in the pathophysiology of MS remain to be elucidated. In the future, researchers must: identify the upstream regulators of Alu RNA expression and editing in MS; validate ADAR-based biomarkers in extensive, independent cohorts of MS; investigate whether therapeutic restoration of Alu editing (utilizing ADAR-recruiting gRNAs) mitigates disease in EAE models; and develop cell-type-specific knockouts of ADAR1 and ADAR2 to differentiate their functions in immune cells compared with CNS-resident cells.

Cerebrovascular diseases

ADAR1 is significantly increased in ischemic stroke lesions, even though astrocytes normally do not produce this enzyme. ADAR1 expression increases dramatically between

day 1 and day 7 after middle cerebral artery occlusion (MCAO) and reperfusion. Loss of ADAR1 is associated with fewer activated astrocytes and microglia, thereby improving neurological outcomes and reducing the extent of cerebral infarction. Mechanistically, ADAR1 induces neuronal death by ROS-mediated production of IL-1β, IL-6, and TNF-α from activated astrocytes and stimulates astrocyte proliferation via the PI3K/Akt pathway. According to these results, ADAR1 is a new regulator that increases astrocyte-driven neuroinflammation, which worsens the consequences of ischemic stroke [78].

ADAR1 p150 expression is significantly increased in microglial cells in the distal MCAO (dMCAO) animal model. Proinflammatory reactions and microglial activation are increased when ADAR1 p150 is overexpressed, but both are decreased when it is knocked down. While preventing its A-to-I RNA editing, ADAR1 p150 knockdown also increases NUPR1, and NUPR1 knockdown reverses the inflammatory response. In dMCAO mice, decreased ADAR1 expression reduces infarct volume, improves neurological outcomes, and attenuates neuroinflammation. These findings suggest that ADAR1 p150 facilitates A-to-I editing of NUPR1, which leads to microglial inflammation and neuronal death [79].

By regulating endothelial responses to IL-6, ADAR2 controls leukocyte transport in inflammatory and ischemic tissues. In vascular endothelial cells, genetic ablation of ADAR2 lowers myeloid cell adherence and rolling on vessel walls as well as immune cell penetration into ischemic areas. The expression of the IL-6 receptor subunit gp130 (IL6ST) and the ensuing IL-6 trans-signaling in endothelium depend on ADAR2. To preserve gp130 expression, ADAR2-induced A-to-I editing mechanistically inhibits Drosha-dependent pri-miRNA processing. Therefore, immune cell trafficking to tissue damage sites is limited by ADAR2 epitranscriptional activity [80].

According to recent research, ADAR1 is pathologically increased in microglia and astrocytes after a stroke, where it encourages neuronal death and neuroinflammation [78, 79]. ADAR2 regulates immune cell trafficking via IL-6/gp130 signaling in endothelial cells, while ADAR1 p150 promotes microglial activation through A-to-I editing of NUPR1[79, 80].

It is necessary to recognize several significant restrictions. First, human translation remains unproven, as most data come from rodent models. Second, it is unknown what cues cause astrocytes and microglia to upregulate ADAR1 after a stroke. Third, no cell-type-specific deletion experiments are available to distinguish ADAR1's functions in astrocytes and microglia. Fourth, the effectiveness of therapeutically targeting ADAR1, such as with inhibitors, within practical therapy windows has not been investigated. Fifth, the role of ADAR2 in additional cerebrovascular disorders has not been investigated. Future studies should confirm the expression and function of ADAR1 and ADAR2 in human post-stroke brain tissue; identify the signaling pathways (such as hypoxia, ROS, or inflammatory cytokines) that induce ADAR1 after stroke; develop ADAR1 knockouts specific to astrocytes and microglia to separate their unique contributions; assess ADAR1 inhibitors or ADAR2-enhancing strategies in delayed treatment windows, such as 6–24 h after stroke; and explore the role of ADAR2 in other conditions such as hemorrhagic stroke or chronic cerebral hypoperfusion.

Psychiatric disorders

Bipolar disorder and GRIK2 editing

Researchers found underediting of glutamate receptor *GRIK2* transcripts at the I/V editing site in individuals with type I BPD. In line with observations of increased intracellular Ca^{2+} levels in patients with BPD, altering this location may alter the channel's Ca^{2+} permeability. The idea that low-level "background" editing improves adaptability and evolvability is supported by the discovery of many new editing sites near known locations; most showed very low editing rates [40].

Schizophrenia: quantitative trait locus (QTLs) and editing regulation

The long intergenic ncRNA (lincRNA) gene *RP11-156P1* is the target of rs146498205, a seed edQTL identified in QTL studies. Among the edQTLs, such as rs146498205, the RNA-binding protein AKAP1 exhibited enhanced binding to the target transcript. AKAP1 is involved in mitochondrial and neuronal control. Every QTL that was found had strong colocalization with schizophrenia and other neuropsychiatric conditions. QTLs were also identified at physiologically relevant genome-wide association study loci, such as *ELAVL2* (ELAV-like RNA-binding protein 2), a crucial tRNA-processing gene associated with schizophrenia risk [81].

ADAR2 downregulation in mood disorders and schizophrenia

Reduced editing of AMPA receptor R/G sites is correlated with lower ADAR2 expression in the postmortem brains of individuals with schizophrenia and bipolar illness. Mice that are heterozygous for $Adar2^{+/-}$ show reduced R/G editing, improved amphetamine-induced hyperactivity, higher locomotor activity in open-field testing, and greater resistance to immobility in forced swimming tests. Importantly, the difference in amphetamine responsiveness between wild-type and $Adar2^{+/-}$ mice was eliminated by an AMPA/kainate receptor antagonist, indicating that these behavioral traits are influenced by decreased ADAR2-mediated editing [82].

Suicide risk: ADARB1, HTR2C, and stressful life events

Polymorphisms in *HTR2C* (rs6318) and *ADARB1* (rs9983925, rs4819035) are linked to suicide attempts (SA). Recent stressful life events, emotional abuse, rs9983925, and rs6318 are independent risk factors for SA; the association between mental illness and emotional abuse is moderated by general trauma. The combined impact of *ADARB1* and *HTR2C* polymorphisms, a diagnosis of a current mood illness, and cumulative exposure to stressful events from infancy and recent times all contribute to SA vulnerability in psychiatric patients [83].

PDE8A editing as a blood-based biomarker for depression and suicide

A-to-I RNA editing of *PDE8A* (phosphodiesterase 8A) is significantly altered in postmortem brain tissue and whole blood samples from individuals with major depressive disorder (MDD) and suicide attempt. By examining several altered isoforms, these editing modifications enabled researchers to differentiate controls from suicide attempt victims. Monitoring PDE8A's RNA editing in blood samples may assist in evaluating depressed symptoms and suicide risk, since PDE8A is associated with immunological responses [84].

ADAR1 regulates BDNF via miR-432 in depression

Through the miRNA miR-432, ADAR1 regulates the expression of brain-derived neurotrophic factor (BDNF). ADAR1 overexpression enhances BDNF protein and downregulates miR-432 in PC12 and SH-SY5Y cells, but ADAR1 underexpression has the opposite effects. An ADAR1 inducer (IFN-γ) recovers decreased brain and serum BDNF levels and reduces depressive-like behavior in chronic unpredictable stress mice models. These results show that antidepressant effects are mediated via the ADAR1/miR-432/BDNF axis [85].

Multiple layers of RNA editing dysregulation are involved in psychiatric disorders, according to current research: underediting of GRIK2 in BPD [40], QTLs targeting editing machinery in schizophrenia [81], reduced ADAR2 expression and AMPA receptor editing in mood disorders [82], variants of ADARB1 and HTR2C linked to suicide risk [83], blood-based PDE8A editing changes as potential suicide biomarkers [84], and the ADAR1/miR-432/BDNF axis in depression [85].

Causality in humans remains unknown, as most research is observational and correlational. Small sample sizes are common. Neurons have never been used to directly assess the functional effects of certain editing modifications, such as GRIK2 I/V or PDE8A. Furthermore, how stress and trauma affect ADAR expression is unknown to us. Additionally, prospective validation is required before blood-based biomarkers may be used in clinical settings. To proceed, researchers should: identify the stress-responsive signaling pathways that regulate ADAR1 and ADAR2; test PDE8A and other blood-based editing biomarkers in long-term patient studies to see whether they predict suicide risk or treatment response; validate key editing changes in large, well-powered postmortem brain cohorts; perform electrophysiology on patient-derived iPSC neurons to see how editing alterations affect neuronal firing and communication; and use animal models with targeted editing tools (such as CRISPR or ADAR-recruiting gRNAs).

Brain tumors

ADAR1 and ADAR2 have conflicting, context-dependent functions in brain malignancies. While ADAR2 is downregulated in glioblastoma (GBM), a malignant tumor, ADAR1 is overexpressed in certain malignancies (such as esophageal, lung, and liver cancers, and leukemia) and promotes tumor development [86]. Current research on several conceptual subjects is summarized in the sections that follow.

ADAR1 promotes tumor growth, immune evasion, and chemoresistance

In cancer cell lines, ADAR1 depletion promotes proinflammatory cytokine production and cancer cell death by relieving PKR inhibition and increasing ISG expression via RIG-I, MDA5, and STING [87, 88]. Notably, in an IFN signaling-dependent way, ADAR1 knockdown makes tumors more susceptible to immune checkpoint blocking (anti-PD-1 treatment) [88, 89]. ADAR1 is overexpressed in GBM and is linked to higher tumor grade and temozolomide (TMZ) resistance. Mechanistically, ADAR1 enhances chemoresistance by promoting TMZ-induced autophagy via p62-mediated selective autophagy, and its expression is associated with a poor prognosis [90]. Furthermore, METTL3, which is overexpressed in GBM, increases ADAR1 protein levels via methylating ADAR1 mRNA. The METTL3/ADAR1 axis is a crucial connection between m6A methylation and A-to-I editing in cancer. ADAR1 then promotes carcinogenesis in a deaminase-independent

way by binding to *CDK2* mRNA, and ADAR1 knockdown prevents glioma development in vivo [91].

Loss of ADAR2 and global editing decline drive aggressive tumor behavior

Approximately 80% of RNA editing events in gliomas are A-to-I conversions, and 96% of these occur within Alu repeats. Compared with normal brain tissue, glioma samples exhibit a global reduction in editing events. The GABRA3 transcript, encoding a GABA receptor subunit, is edited at c.1026 A > G (p.I343M) in 73% of control samples; however, editing at this site declines progressively in low-grade gliomas (LGGs) and is lowest in GBM. This editing event stabilizes the GABRA3 transcript and reduces glioma cell migration and invasion. Conversely, the unedited transcript is less stable and correlates with more aggressive tumor behavior [42]. Contrary to previous beliefs, low ADAR2 protein is associated with a poor prognosis; not all GBM tissues have low ADAR2 levels. Reducing endogenous ADAR2 confirms ADAR2 as a crucial deaminase and prognostic marker in GBM by promoting anchorage-independent growth, enhanced migration, and cell proliferation [92].

Noncoding RNAs and editing-dependent pathways regulate metabolism and therapy response

The prognosis for GBM, a very aggressive brain tumor, is dismal. Glycolipid metabolism is closely linked to GBM development and its malignant characteristics. However, the exact roles of ADARs and snoRNAs in glycolipid metabolism in GBM cells remain unknown. In GBM, the SNORD113-3/ADAR2/PHKA2/EBF1 pathway regulates glycolipid metabolism and tumor progression. SNORD113-3 upregulates ADAR2 by promoting homodimerization. ADAR2 then edits PHKA2 mRNA, and PHKA2 phosphorylates EBF1 at Y256, reducing its stability and expression. EBF1 normally suppresses PKM2 and ACLY expression. In xenograft models, overexpression of ADAR2, SNORD113-3, or PHKA2 halted tumor progression, suggesting that targeting this pathway may improve GBM prognosis [93]. The miR-589-3p is nearly 100% edited in healthy brain tissue but shows reduced editing in GBM. ADAR2 facilitates editing of miR-589-3p, redirecting it from the tumor suppressor *PCDH9* to the proinvasive metalloproteinase *ADAM12*. The unedited form promotes GBM cell migration, invasion, and proliferation, while the edited version suppresses these malignant traits [94]. In glioma cells that are resistant to TMZ, the lncRNA *ATXN8OS* is downregulated. It binds to ADAR, which stabilizes GLS2 mRNA, thereby promoting ferroptosis and reducing TMZ resistance. Therefore, one possible target for reducing chemotherapeutic resistance is the ADAR/GLS2 pathway [95]. Additionally, the lncRNA *BDNF-AS* is downregulated in GBM, and its overexpression increases apoptosis and reduces tumor growth by stabilizing p53 mRNA in cooperation with ADAR. p53 also transcriptionally activates *BDNF-AS*, creating a positive feedback loop that suppresses tumor growth [96].

Prognostic signatures and clinical correlations

Inconsistent relationships between ADAR1 mRNA and protein expression were found in a pan-cancer study. Patients with LGG were divided into high- and low-risk groups using a three-gene signature (*ADAR*, *HNRNPK*, and *SMG7*). High-risk patients had lower overall survival, a higher tumor grade, and more noncoding mutations. Immune

infiltration had an inverse correlation with this signature. Patient outcomes were associated with promoter hypermethylation and upstream regulators SPI1 and miR-206 [97].

Recent research indicates that ADAR1 and ADAR2 have contrasting, context-dependent functions in brain tumors: ADAR1 overexpression facilitates tumor proliferation, immune evasion, and resistance to chemotherapy [86–91, 97], whereas ADAR2 deficiency is associated with increased malignancy [42, 92–94]. Principal mechanisms include the loss of GABRA3 editing [42], METTL3 control of ADAR1 [91], BDNF-AS/ADAR/p53 feedback [96], miR-589-3p editing [94], and ferroptosis regulation via ATX-N8OS/ADAR/GLS2 [95].

Key limitations include: no clinical trials of ADAR-targeted therapeutics in GBM; most evidence from cell lines/xenografts (little human validation); unproven causation; and potential conflicts between ADAR1's involvement in autophagy-driven chemoresistance and IFN-driven immune evasion. Future priorities include developing ADAR2 restoration strategies (gene therapy, gRNAs), testing ADAR1 inhibitors/ADAR2 enhancers in orthotopic models, evaluating synergy with TMZ or checkpoint inhibitors, validating editing changes (GABRA3, miR-589-3p) in large human cohorts, and investigating editing-based biomarkers for GBM diagnosis/prognosis.

Other CNS disorders

Sepsis-associated encephalopathy (SAE)

A-to-I RNA editing activity in cerebral arteries is dynamically altered by acute neuroinflammation in SAE. Differential RNA editing processes impacting genes such as *Meg3* (lincRNA), *Azin1* (missense editing), *Ggps1*, and *Gch1* were found in cerebral endothelial cells, microglia, and cerebral arteries. A-to-I editing may contribute to the pathophysiology of SAE, as evidenced by the strong correlation between edited gene expression and time since LPS administration [98].

Post-traumatic stress disorder (PTSD)

RNA editing of the serotonin receptor *HTR2C* (5-HT2CR) transcript causes dynamic alterations in ADAR and ADARB1 expression in the central amygdala (CeA) of an animal model of PTSD. ADAR enzymes deaminate 5-HT2CR, thereby lowering agonist affinity, G protein coupling, and serotonin signaling. Significantly, a single intra-CeA injection of a 5-HT2CR antagonist significantly decreased PTSD-like symptoms for 3 weeks, indicating that this editing mechanism may be therapeutically beneficial [38].

Developmental and epileptic encephalopathy (DEE) from ADARB1 mutations

Three siblings with severe DEE were found to have bi-allelic *ADARB1* mutations, identified using exome sequencing: a deletion *c.1245_1247+1del* (*p.Leu415PhefsTer14*) and a missense variation *c.1889G>A* (*p.Arg630Gln*). While the missense variant significantly reduces ADAR2 enzymatic activity in vitro, the frameshift mutation introduces an early stop codon, resulting in enzyme inactivation. The critical function of ADAR2 in brain development was highlighted by the patients' microcephaly, severe intellectual impairment, axial hypotonia, and uncontrollable early infantile seizures [49].

Seizure-induced downregulation of ADARs in the developing brain

ADAR1 and ADAR2 mRNA expression was dramatically decreased in the developing brain 24–72 h following seizure activity in a newborn mouse model of multiple pilocarpine-induced seizures. This was associated with increased apoptosis in certain brain areas and a decreased ratio of *Gria2* and *Gria4* to total AMPA receptor subunit mRNA. These results point to AMPA receptor editing as a possible neuroprotective target and imply that age-dependent loss of GluA2 editing contributes to seizure-induced excitotoxicity [99].

ADARB1 mutations in microcephaly, intellectual disability, and epilepsy

Bi-allelic *ADARB1* mutations, including variations in the dsRNA-binding domain and close to the deaminase region, were found in four unrelated individuals with microcephaly, intellectual impairment, and epilepsy. One mutation changed *ADARB1* splicing, and functional tests verified decreased *ADAR2* editing activity on known substrates. These findings highlight the crucial function of RNA editing in brain development and confirm *ADARB1* as a hereditary etiology of neurodevelopmental diseases [50] (Table 3).

Recent research broadens the implications of ADAR dysregulation to other CNS disorders: SAE entails dynamic modifications in cerebral vasculature [98]; PTSD is characterized by modified HTR2C editing in the amygdala [38]; DEE and associated neurodevelopmental abnormalities result from bi-allelic *ADARB1* mutations [49, 50]; and newborn seizures lead to decreased ADAR expression and GluA2 editing [99].

The majority of the data are derived from extremely small patient groups or animal models. Researchers still need to demonstrate that editing modifications are the real cause of illness rather than only a correlation. The use of 5-HT2CR antagonists for PTSD is one example of a therapeutic method that has not progressed beyond preclinical stages. Furthermore, the mechanism by which seizures result in decreased ADAR expression remains unknown to us. Future research should confirm SAE editing changes in larger human studies; investigate whether manipulating 5-HT2CR editing can prevent or reverse PTSD symptoms in additional animal models; screen for *ADARB1* mutations in patients with intellectual disability and unexplained DEE; ascertain whether restoring ADAR expression or GluA2 editing can protect the brain from damage caused by seizures; and investigate methods to enhance ADAR2 function in neurodevelopmental disorders caused by partial loss of this enzyme.

Emerging therapeutic opportunities

Reversible and perhaps safer than permanent CRISPR-based DNA editing, ADAR-mediated RNA editing offers a potential treatment option for CNS diseases. The two primary approaches employed today are (1) providing exogenous ADAR domains coupled to recruitment modules and (2) recruiting endogenous ADAR enzymes utilizing modified gRNAs. Every strategy has unique benefits, drawbacks, and delivery issues [101, 102].

Strategies for recruiting endogenous ADARs (LEAPER, CLUSTER, and MIRROR)

By providing synthetic gRNAs that base pair with target mRNAs to create a dsRNA substrate that attracts ADARs to convert a particular adenosine to inosine, these technologies leverage the cell's own ADAR enzymes [101–103].

Table 3 The role of ADAR-mediated RNA editing in CNS disorders

CNS disorders	Primary ADAR involved	Key RNA editing defect	Consequence	Proposed role	Ref
AD	ADAR1, ADAR2	ADAR2 downregulation and loss of Alu RNA editing in the hippocampus and hippocampal vasculature	Innate immune activation via NF-κB/IFN pathways; synaptic protein dysregulation	Modifier (exacerbates neuroinflammation)	[39, 63, 64]
ALS	ADAR2	ADAR2 mislocalization in C9orf72 ALS; GRIA2 Q/R underediting in 44–56% of motor neurons	Increased Ca^{2+} flux through AMPA receptors leads to excitotoxicity, coupled with genome-wide editing defects	Driver (motor neuron death)	[65, 66, 100]
PD	ADAR1, ADAR2, ADARB1	A-to-I editing was reduced globally, ADAR expression was downregulated, and miRNA regulation was changed	Dysregulation of NMD; neuroinflammation	Modifier (contributes to pathogenesis)	[70, 71, 73]
MS	ADAR1, APOBEC	Decreased ADAR and APOBEC activity; decreased Alu RNA editing	IFN and NF-κB activation via RIG-I/TLR-3; protein synthesis impairment	Modifier (drives autoimmunity)	[76, 77]
Cerebrovascular diseases (stroke)	ADAR1, ADAR2	ADAR2 reduction in the endothelium and ADAR1 overexpression in astrocytes and microglia	ROS-induced secretion of IL-1β, IL-6, and TNF-α promotes neuronal loss, coupled with defective trafficking of immune cells	Driver (exacerbates injury)	[78, 80]
BPD	ADAR2	GRIK2 underediting at I/V site	Altered Ca^{2+} permeability of kainate receptors	Modifier (contributes to mood dysregulation)	[40]
MDD	ADAR1, ADARB1	PDE8A editing alters blood and brain; ADAR1 controls BDNF via miR-432	Altered cAMP signaling; reduced BDNF expression	Biomarker (PDE8A); driver (ADAR1/miR-432/BDNF axis)	[84, 85]
Glioma (LGG/GBM)	ADAR1, ADAR2	ADAR1 overexpression; ADAR2 downregulation; GABRA3 editing loss; miR-589-3p hypo-editing	Increased invasion and migration; autophagy-based TMZ resistance; alteration of glycolipid metabolism	Driver (tumor progression); biomarker (prognostic)	[42, 90, 93, 94]
PTSD	ADAR1, ADARB1	Altered HTR2C (5-HT2CR) editing in the central amygdala	Reduced serotonin signaling, G-protein coupling, and agonist affinity	Modifier (affects resilience)	[38]
DEE	ADAR2 (ADARB1)	Bi-allelic *ADARB1* mutations (*p.Arg630Gln*, *p.Leu415PhefsTer14*)	Severely impaired ADAR2 enzymatic activity	Driver (monogenic cause)	[49]

LEAPER employs short ADAR-recruiting RNAs (arRNAs), either chemically synthesized or virally delivered, that create an A–C mismatch at the target adenosine. This approach achieves editing efficiencies of up to 80% across various human primary cell types with minimal off-target effects. Importantly, LEAPER restored α-L-iduronidase activity in fibroblasts from patients with Hurler syndrome without triggering innate immune responses, highlighting its therapeutic promise for genetic disorders [104].

Clustered ADAR-recruiting gRNAs for effective RNA editing (CLUSTER) improves upon earlier designs by incorporating clusters of single-stranded recruiting segments (RS elements) that bind to distinct, distant regions of the target mRNA. Unlike LEAPER, which extends the specificity domain, CLUSTER uses multiple gRNAs that bind neighboring regions, raising the local concentration of ADAR enzymes at the target site for

more precise and efficient editing. Preclinical studies report 45% editing efficiency in cell culture (excluding bystander edits) and up to 10% editing in mouse liver following hydrodynamic tail-vein delivery. This approach is particularly suited for correcting complex mutations or editing multiple sites within a single transcript [105].

By leveraging structural motifs from highly edited endogenous Alu repeats, the mimicking inverted repeats to recruit ADARs using engineered oligoribonucleotides (MIRROR) technique is a logical gRNA design strategy that improves ADAR-mediated base editing [106]. MIRROR takes advantage of the poorly paired structures found in inverted Alu repeats in human tissues, recognizing that precisely matched dsRNA is a poor substrate for ADAR. In human cells and primary hepatocytes from an alpha-1 antitrypsin-deficient mouse model, MIRROR increased editing efficiency by 5.7-fold compared with traditional designs using synthetic oligoribonucleotides that imitate these natural substrates [107].

ADAR-recruiting gRNAs can be delivered either as chemically synthesized or in vitro-transcribed antisense oligonucleotides (ASOs) or as DNA-encoded gRNAs using viral or nonviral vectors. The choice of delivery mechanism depends on the disease, tissue, and cell type. DNA-encoded gRNAs offer advantages over ASOs: They are transcribed endogenously, provide long-lasting expression, face no size constraints, and allow customization via promoters and regulatory elements, making them attractive for treating terminally differentiated cells, such as neurons, with a single injection [108]. However, unlike ASOs, DNA payloads cannot be "turned off" if adverse events occur, and they carry risks of immunogenicity and activation of the DNA-sensing pathway. Regardless of delivery method, ADAR's intrinsic sequence preferences and promiscuous activity make engineering gRNA efficiency and specificity challenging. Delivering therapeutics to the correct CNS cell types remains a major hurdle for both approaches, underscoring the need for continued innovation in delivery technologies [108].

Strategies for delivering exogenous ADAR domains (SNAP-ADAR and RtABE)

These methods not only provide greater control over editing specificity by delivering exogenous ADAR deaminase domains linked to protein- or RNA-recruitment modules, but they also raise concerns about immunogenicity [109, 110].

SDRE techniques redirect ADAR activity to convert specific adenosines to inosine, thereby correcting premature termination codons (UAG, UAA, and UGA) and restoring protein function [109, 111] (Fig. 6). SNAP-ADAR method fuses the ADAR2 deaminase domain to the SNAP-tag enzyme, which forms a covalent bond with a benzylguanine (BG)-modified gRNA. The gRNA guides the SNAP-ADAR complex to the target transcript. Using a hyperactive *ADAR2* mutant, SNAP-ADAR achieves up to 90% editing efficiency in cells and embryos, making it one of the most efficient SDRE systems available [109, 112, 113]. Compared with DNA editing, SDRE offers several advantages: Transient effects reduce the risk of permanent off-target changes, and smaller component sizes simplify delivery, especially when using a single antisense gRNA to recruit endogenous ADARs. However, challenges remain, including poor RNA stability and innate immune activation by unmodified RNAs. Chemical modifications and embedding gRNAs in circular RNAs (which can improve stability by weeks) offer potential solutions [109].

The RNA transformer adenosine base editor (RtABE) was designed to overcome off-target risks associated with ectopic ADAR expression. RtABE consists of an ADAR

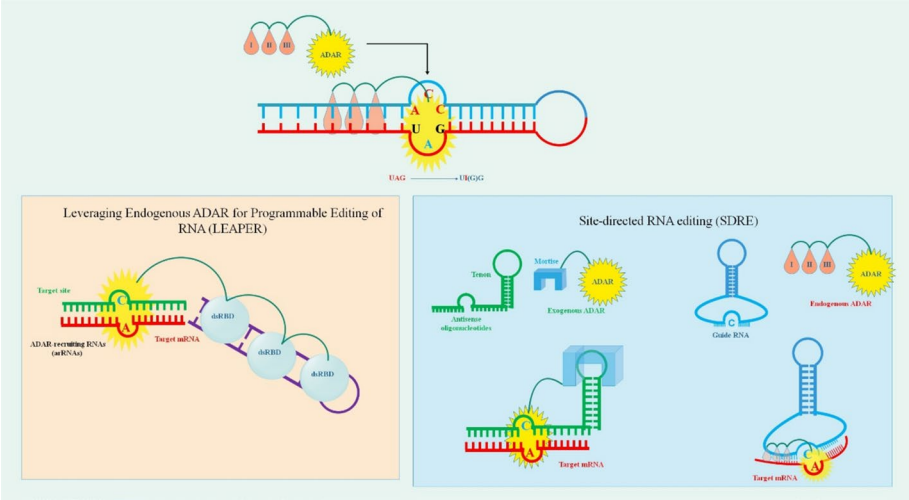


Fig. 6 Many SDRE approaches have been developed to adaptively target disease-causing point mutations by leveraging ADARs' catalytic adenosine deamination capabilities. An adenosine–guanine transition is the building block of A-to-I RNA editing [115]. This figure was created using EdrawMax software

inhibitor (ADI) fused to the ADAR2 deaminase domain (ADAR2DD), rendering the enzyme inactive until it reaches its intended target. Upon gRNA-mediated target binding, the ADI is cleaved, activating ADAR2DD. RtABE efficiently edits various sequence contexts, including UAN, AAN, MAY, and GAN. AAV delivery of RtABE to Hurler syndrome mice restored α-L-iduronidase activity with minimal off-target effects, highlighting its potential as a safe, targeted RNA editing system [114].

Exogenous domain approaches require delivery of both the gRNA and the ADAR fusion protein (typically via AAV or mRNA). These methods not only provide improved control of specificity, but they also carry the risk of off-target editing by the constitutively active deaminase and immunogenicity against the foreign protein domains [108].

Small-molecule modulators and regulatory mechanisms

Pharmacological manipulation of ADAR activity is an emerging therapeutic approach that goes beyond gRNA-based approaches. Fluoxetine (Prozac) modifies ADAR editing at the serotonin receptor HTR2C in mice, suggesting that certain CNS medications may act in part by modulating ADAR [116]. The alkylating compound *N*-ethylmaleimide and the zinc chelator *O*-phenanthroline are known ADIs [117]. Furthermore, ADAR editing levels in neurons are regulated by the RNA-binding protein Zn72D (and its mammalian analog Zfr), indicating possible targets for indirect control of editing activity [117, 118].

The OAS–RNase L system is an IFN-inducible antiviral pathway activated by viral dsRNA. ADAR1 normally prevents OAS activation by editing dsRNA, but *ADAR1* mutations cause AGS, an interferonopathy where ADAR1 insufficiency leads to RNase L activation and cell death [119]. To explore RNase L as a therapeutic target for AGS, researchers screened 500 protein kinase inhibitors and identified EA and valonic acid dilactone (VAL) as selective inhibitors of RNase L. VAL showed 100-fold greater selectivity for RNase L over the related protein IRE1. Although EA and VAL are ATP-competitive inhibitors of CK2, they do not bind RNase L's pseudokinase domain. VAL rescued cell death caused by ADAR1 deletion, albeit with 1000-fold reduced potency, providing a framework for developing RNase L-targeted therapies for AGS [119].

Therapeutic potential for cancer

Endogenous ADAR may repair cancer-causing mutations. Endogenous ADAR might repair at least one driver mutation in over one-third of somatic cancer samples and reverse one-fifth of germline single-nucleotide variations in cancer risk genes. This strategy is appealing for cancer treatment because it can deliver modest payloads [105].

By permitting the buildup of endogenous dsRNA, which stimulates MDA5/PKR and IFN-I responses and enhances $CD8^+$ T cell and NK cell infiltration, ADAR1 inhibition has a dual "two-hit" effect: It causes intrinsic cancer cell death and reactivates antitumor immunity [120]. ADAR1 deletion slows tumor development and increases survival in immunocompetent GBM models. By preventing autophagy, ADAR1 knockdown also makes glioma cells more susceptible to TMZ [95]. ADAR1i-124 and other small-molecule inhibitors have synergistic effects when combined with immune checkpoint blockade or epigenetic treatments such as 5-Aza-CdR. Restoring ADAR2 activity, however, may prevent glioma formation, as it functions as a tumor suppressor in the brain. Developing blood–brain barrier (BBB)-crossing, brain-accessible ADAR1 inhibitors remains a major challenge [121, 122] (Table 4).

The status and challenges of clinical translation

Clinical studies for ADAR-mediated RNA editing treatment have not yet been conducted for CNS diseases. Most research on LEAPER and CLUSTER is limited to cell culture or mouse models (mostly liver), and both remain in the preclinical stage [104, 105]. Hurler syndrome mice have been used to test RtABE, but models of CNS diseases

Table 4 Comparison of ADAR-mediated RNA editing platforms: mechanisms, delivery, efficiency, and CNS readiness

Platform	Mechanism	Delivery	Editing efficiency	Key advantage	Off-target risk	CNS readiness	Ref
LEAPER	Endogenous ADAR recruitment via arRNA	ASO or viral	Up to 80%	No foreign proteins; low immunogenicity	Low	Requires CNS delivery optimization	[104]
CLUSTER	Multiple gRNAs clustering RS elements	Hydrodynamic (liver); needs CNS optimization	45% (cell), 10% (in vivo)	Precise multisite editing	Low	Not yet tested in CNS	[105]
MIRROR	Alu repeat-mimicking structures	Synthetic oligos	5.7 × improvement	Rationally designed natural mimics	Not reported	Not yet tested in CNS	[107]
SNAP-ADAR	ADAR2dd + BG-gRNA covalent link	Protein + gRNA	Up to 90%	Highly efficient; hyperactive mutant	Moderate (active deaminase)	Requires delivery to CNS	[109, 112, 113]
RtABE	ADI-ADAR2dd fusion; cleavage-activated	AAV + gRNA	Effective across contexts	Conditional activation; low off-target	Low (conditional activation)	AAV can target CNS	[114]

have not yet been used [107]. Delivery across the BBB and the absence of proven CNS disorder targets where temporary editing is the best therapeutic approach are the main obstacles. Clinically, the most sophisticated RNA editing techniques target retinal problems (e.g., EDIT-101 for *CEP290* mutations), which might lead to CNS uses [123, 124].

Delivery across the BBB

There are several ways to provide ADAR-based treatments to the CNS. After systemic administration, viral vectors, especially recombinant adeno-associated viruses (rAAVs) such as AAV9 and AAVrh.10, can cross the BBB and achieve widespread transduction of neurons and astrocytes, providing long-term expression but encountering difficulties with pre-existing immunity and off-target transduction of peripheral organs [125, 126]. Lipid nanoparticles (LNPs), exosomes, and polymeric nanoparticles are examples of nonviral platforms with higher payload capacity and lower immunogenicity; however, they currently have limited CNS bioavailability after systemic injection [127]. The BBB is completely circumvented by local administration routes such as intrathecal (IT), intracerebroventricular (ICV), and intraparenchymal, thereby reducing peripheral exposure and enabling direct CNS targeting. However, these methods are invasive, necessitate surgical skill, and may not achieve widespread CNS distribution [128, 129]. Although it requires active transport across the BBB or temporary disruption of the BBB, systemic administration remains the most practical choice. A potential method for safely and temporarily opening the BBB to transport nanoparticles and even large molecules, such as LNPs containing siRNA or mRNA, is focused ultrasound in conjunction with microbubbles [128–130].

Off-target editing

There are certain off-target issues with ADAR-based editing. ADARs are naturally promiscuous enzymes that modify many adenosines within dsRNA, in contrast to CRISPR, which targets DNA. Unintentional A-to-I conversions may result from engineered gRNAs unintentionally recruiting ADARs to transcripts with limited sequence complementarity. Off-target alterations are more common than previously reported in focused analyses, according to transcriptome-wide studies using unbiased detection techniques such as RNA-seq. Furthermore, it is particularly difficult to distinguish therapeutic edits from spontaneous editing events, as the brain produces large quantities of endogenous ADARs [131]. Compared with permanent DNA changes, the temporary nature of RNA editing somewhat reduces the risk of off-target effects; however, repeated doses required for persistent CNS disorders may eventually increase that risk. Optimizing gRNA design (CLUSTER, MIRROR), using conditionally active systems (RtABE), and adding chemical modifications to improve specificity are methods for reducing off-target editing [123, 124, 131].

Immunogenicity

The safety and effectiveness of gene treatments are seriously threatened by the immunogenicity of gRNAs and viral vectors employed for ADAR systems in the CNS. Although the CNS was formerly thought to be "immune privileged," it is now known that viral vectors and therapeutic payloads (such as gRNAs/ADAR components) can elicit innate and adaptive immune responses [132, 133]. Unmodified gRNAs trigger inflammatory

responses by activating innate immune sensors (TLR-3, TLR-7, TLR-8, and RIG-I); chemical modifications such as 2′-*O*-methyl, phosphorothioate, and locked nucleic acids reduce immunogenicity but may compromise editing efficiency [134, 135]. In addition, 50–70% of people have pre-existing neutralizing antibodies against AAV, which limit eligibility and repeat dosing for viral vectors. AAV genomes can induce p53-dependent DNA damage and MAVS-dependent IFN-I responses, which may result in neurotoxicity even in the CNS [136–138]. Although systemic exposure is decreased by direct CNS delivery (IT or ICV), localized inflammation may still occur. Long-term production of foreign bacterial proteins may elicit adaptive T cell responses for exogenous ADAR domain delivery, such as dCas13-ADAR. Prophylactic immunosuppression, such as corticosteroids; the creation of novel AAV capsids with lower immunogenicity; the use of cell-type-specific promoters (strong in neurons, weak in antigen-presenting cells); and the use of chemical modifications or circular RNA designs to reduce gRNA-mediated innate immune activation are among the mitigation strategies [136–139].

Reversibility and dosing for chronic disease

RNA editing's transient nature is a double-edged sword: While it offers a safety benefit over permanent DNA editing by reducing the risk of irreversible off-target effects [101–103], this transience may require repeated dosing to sustain therapeutic benefit in chronic, progressive conditions such as AD, PD, and ALS. For most ADAR platforms, dosing frequency is unknown; however, ASO-based methods, such as nusinersen for spinal muscular atrophy, have established clinical precedent for IT injections every 4 months following a loading-dose regimen [140–142]. AAV-delivered gRNAs provide longer-lasting expression but are difficult to reverse if adverse events arise, and hyperactive ADAR variants have been shown to cause off-target toxicity in vivo [143, 144]. New optimization techniques include chemical modifications and circular RNA scaffolds that can prolong the half-life of gRNA, as well as tunable systems such as small-molecule-controlled ADAR activation via aptazyme-based gRNAs, which allow conditional turn-on or turn-off of editing activity [117, 118]. Notably, following a single systemic AAV injection, a designed U7 small nuclear RNA scaffold recently achieved 75% RNA editing in the mouse brain, indicating the possibility of long-lasting, one-time CNS administration [145]. Whether temporary correction of a single editing event, such as restoring GRIA2 Q/R editing in ALS, would provide long-term clinical benefit or whether ongoing disease pathology would quickly re-establish the editing defect, necessitating repeated or continuous intervention, is a crucial unanswered question. To address this issue, longitudinal research on chronic illness models is urgently needed [65, 146].

Regulatory considerations

RNA editing medicines pose particular challenges for regulatory clearance because they are highly mechanism-specific and require tailored evaluations. Orphan illnesses, or uncommon ailments, are appealing first targets for RNA editing therapies because they offer a more flexible regulatory pathway with less stringent investigational new drug criteria. To ensure safety and effectiveness, proactive cooperation with regulatory bodies remains necessary [101, 102]. Species-specific variations in RNA transcripts and ADAR expression provide a significant translational challenge. Nonhuman primates (NHPs) are used to recreate human disease states with high precision, since therapies intended for

Table 5 Key unresolved challenges for clinical translation of ADAR-mediated RNA editing

Challenge category	Current status	Key barrier	Mitigation strategy	Ref
Clinical trial status	No CNS trials; retinal programs (EDIT-101) most advanced	Lack of validated CNS targets; delivery	Target orphan CNS diseases first	[104, 105, 123, 124]
BBB delivery	AAV9/rh10 (systemic); IT/ICV (local); focused ultrasound (emerging)	Pre-existing immunity; invasive local routes	Engineered capsids; combination approaches	[125, 126, 128–130]
Off-target editing	Unbiased methods reveal more edits than targeted analyses	High endogenous ADAR in the brain; no standardized metrics	CLUSTER, MIRROR, RtABE; chemical modifications	[123, 124, 131]
Immunogenicity	Pre-existing AAV antibodies (50–70%); TLR activation by gRNAs	Neurotoxicity from AAV genomes; repeat dosing limitations	Immunosuppression; novel capsids; circular RNAs	[136–139]
Reversibility/dosing	Transient editing = safety advantage, but may require repeat dosing for chronic disease	Unknown durability in progressive neurodegeneration	Tunable systems; longitudinal chronic disease models	[101–103, 140–142]
Regulatory	Orphan drug pathways offer flexibility; NHP studies are often needed	Species-specific transcript differences	Humanized systems (organoids); early Food and Drug Administration (FDA) engagement	[101, 102]

human use often fail in standard mouse models. Variations in the whole transcriptome may result in different off-target effects across species, even when editing sites are conserved. To close this gap, scientists are combining preclinical NHP research with sophisticated humanized systems, such as organoids and human-derived cells, in accordance with legal criteria for creating safe and efficient treatments [101, 102] (Table 5).

Outstanding questions and future directions

Compared with CRISPR-based DNA editing, RNA editing has several benefits, including the use of endogenous human enzymes rather than immunogenic bacterial proteins, effectiveness in nondividing cells (including neurons), and temporary effects that reduce the risk of lasting off-target modifications [111, 147]. However, these same characteristics, transience and reversibility, become constraints for long-term neurodegenerative illnesses that need ongoing treatment. The important issue is not whether technology is "better" but which technique is more appropriate for a given medical setting. While early onset monogenic illnesses may be best suited to permanent DNA correction, acute situations (e.g., stroke, damage) may be best suited to transient RNA editing.

Three of the seven unanswered questions have been identified as a major priority. First, what distinguishes ADAR1 from ADAR2 in terms of spatiotemporal specificity across cell types, developmental stages, and brain regions? Second, is it possible to create noninvasive biomarkers (based on EV or cerebrospinal fluid [CSF]) to track brain ADAR activity? Third, and perhaps most importantly, how can we plan clinical trials when pharmacodynamic readouts of CNS editing levels are unavailable? Fourth, does persistent neurodegeneration in ALS, AD, and PD need the temporary repair of a single editing event? What is the therapeutic window for ADAR modulation without interfering with normal editing functions? This is the fifth crucial issue. Sixth, which CNS conditions—such as Hurler syndrome, DEE, or AGS—are the best first-in-human targets?

Seventh, how might species-specific variations in ADAR expression and RNA transcripts be reconciled? Whether ADAR editing can effectively go from the bench to the bedside for CNS disorders will depend on how these issues are resolved, especially the crucial issues of trial design and treatment window.

The seeming conflicts in the field may reflect the underlying complexity of biology. While ADAR1 is pathogenic in ischemic stroke (gain-of-function exacerbates damage), it exhibits a protective role in AGS (loss-of-function causes illness) [119]. When cell type (microglia versus astrocytes), illness phase (acute versus chronic), and molecular context are taken into account, this is resolved. Similarly, in ADAR2 knockout mice, GRIA2 underediting is fatal, although causation in sporadic ALS is still correlational. To settle this argument, adult conditional rescue trials are critically required [65, 146].

To get ADAR editing closer to clinical use, several related issues need to be resolved. Because genuine A-to-I conversions must be distinguished from sequencing errors and natural genetic variation, accurately identifying true RNA editing events remains challenging in RNA-seq data; single-cell and spatial transcriptomics will be crucial for revealing cell-type-specific editing patterns that bulk tissue analyses miss [148–150]. Another challenge is the complexity of ADAR1, which regulates the transcriptome through RNA binding, catalytic editing, and protein interactions—functions that are difficult to target therapeutically. Targeting ADAR1 in CNS disorders requires careful weighing of benefits against risks, as ADAR1 is also overexpressed in several cancers [6]. Since miRNA expression, mRNA targeting, and editing levels differ significantly across cell types even within the same tissue, spatiotemporal specificity adds further complexity. Safe, editing-based treatments will require comprehensive knowledge of this heterogeneity [151]. Because brain and spinal cord biopsies are not practical for pharmacodynamic readouts, validated surrogate endpoints such as CSF editing levels, blood-based EV biomarkers, functional imaging, or sensitive clinical outcome measures that align with regulatory agencies are required for clinical trial design [152]. To ensure that developing tools meet practical requirements and are accepted in clinical practice, effective translation requires early and ongoing participation from patient groups, doctors, and commercialization partners [151].

Five objectives must be prioritized to accelerate clinical translation. To allow noninvasive pharmacodynamic monitoring, first validate CSF and EV-based editing biomarkers within 2–3 years. Second, within 3–4 years, develop adult conditional rescue models for GRIA2 editing to prove causation in chronic neurodegeneration. Third, within 3–5 years, create cell-type-specific *ADAR1* and *ADAR2* knockouts to analyze cellular contributions. Fourth, within 5–7 years, create isoform-selective, brain-penetrant small-molecule ADAR modulators as a substitute for genetic delivery. Fifth, use the monogenic etiology and regulatory flexibility of an orphan CNS editing condition (AGS, DEE, or Hurler syndrome) to initiate first-in-human trials within 5–7 years.

ADAR-based RNA editing technologies have the potential to significantly impact biotechnology and medicine when paired with evolving delivery methods. Many CNS disorder situations are ideally suited to the intrinsic benefits of RNA-based therapies, including tunability, reversibility, and temporary off-target effects. However, to fully realize this promise, mechanistic interventional research, validated biomarkers, and careful clinical trial design are needed, alongside descriptive investigations. The field

may overcome the translational gap and provide first-in-class treatments for currently incurable neurological illnesses by prioritizing the unanswered concerns mentioned above [152].

Conclusions

The molecular processes underlying CNS diseases have been elucidated through RNA editing research, providing promising new avenues for diagnostics, prognosis, and therapy. Further research is necessary to expand the global editing profiles for various CNS disorders, as existing data are primarily descriptive. RNA editing techniques that utilize ADAR substrates introduce additional functional complexity, and RNA editing acts as a mediator between the epigenome and environmental signals.

The complex regulatory network of ncRNAs (including lncRNAs and miRNAs), along with RNA editing and modification, contributes to a common thread of RNA-mediated regulatory circuitry necessary for proper brain function. ADAR enzymes, particularly ADAR1 and ADAR2, affect a wide range of neurological disorders through their pivotal role in CNS RNA editing.

Although ADAR editing has been associated with various CNS disorders such as AGS, neurodegenerative diseases, and epilepsy, therapeutic intervention remains challenging owing to the complexity of ADAR editing and the large number of substrates it affects. Moreover, whether editing of repetitive RNA sequences or other noncoding regions contributes to the pathophysiology of human CNS disorders remains an open question.

Translating ADAR editing into clinical practice faces substantial challenges owing to its complex mechanisms and technological limitations, underscoring the need for continued research and development in RNA editing technology as well as further clinical trials to determine safety and efficacy.

Abbreviations

AD	Alzheimer's disease
ADAR	Adenosine deaminase acting on RNA
ADI	ADAR inhibitor
AGS	Aicardi–Goutières syndrome
ALS	Amyotrophic lateral sclerosis
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APOBEC	Apolipoprotein B mRNA editing enzyme
ASD	Autism spectrum disorder
ASO	Antisense oligonucleotide
A-to-I	Adenosine-to-inosine
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
BG	Benzylguanine
BPD	Bipolar disorder
CAG	Cytosine–adenine–guanine
CeA	Central amygdala
CNS	Central nervous system
CSF	Cerebrospinal fluid
DEE	Developmental and epileptic encephalopathy
dMCAO	Distal middle cerebral artery occlusion
dsRBD	Double-stranded RNA binding domain
dsRNA	Double-stranded RNA
EA	Ellagic acid
EAE	Experimental autoimmune encephalomyelitis
edQTL	*cis*-Editing quantitative trait locus
EV	Extracellular vesicle
FTD	Frontotemporal dementia
GBM	Glioblastoma
gRNA	Guide RNA
HRE	Hexanucleotide repeat expansion
ICV	Intracerebroventricular

IFN	Interferon
iPSC	Induced pluripotent stem cell
ISG	Interferon-stimulated gene
IT	Intrathecal
LEAPER	Leveraging endogenous ADAR for programmable editing of RNA
LGG	Low-grade glioma
lincRNA	Long intergenic noncoding RNA
lncRNA	Long noncoding RNA
LNP	Lipid nanoparticle
MAVS	Mitochondrial antiviral signaling protein
MCAO	Middle cerebral artery occlusion
MDA5	Melanoma differentiation-associated protein 5
MDD	Major depressive disorder
MIA	Maternal immune activation
MIRROR	Mimicking inverted repeats to recruit ADARs using engineered oligoribonucleotides
miRNA	MicroRNA
MS	Multiple sclerosis
ncRNA	Noncoding RNA
NES	Nuclear export sequence
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHP	Nonhuman primate
NLS	Nuclear localization sequence
NMD	Nonsense-mediated decay
OAS	2′-5′-Oligoadenylate synthetase
PD	Parkinson's disease
PKR	Protein kinase R
pri-miRNA	Primary microRNA
PTSD	Post-traumatic stress disorder
QTL	Quantitative trait locus
rAAV	Recombinant adeno-associated virus
RIG-I	Retinoic acid-inducible gene I
RNA-seq	RNA sequencing
ROS	Reactive oxygen species
RtABE	RNA transformer adenosine base editor
SA	Suicide attempt
SAE	Sepsis-associated encephalopathy
SDRE	Site-directed RNA editing
STING	Stimulator of interferon genes
TLR	Toll-like receptor
TMZ	Temozolomide
VAL	Valonic acid dilactone
ZBD	Z-DNA binding domain

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Declarations

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