Mediterranean Journal of Medicine & Medical Sciences
ISSN: 3107-2720
Mediterr J Med Med Sci
doi: 10.5281/zenodo.0000000
https://mmj.org.ly

REVIEW article

Autism in the era of gene editing: A CRISPR-Cas9 review

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Received: 22-05-2026, **Accepted:** 29-06-2026, **Published online:** 00-00-2026

HOW TO CITE THIS
Arjun N, Bhat R. Autism in the era of gene editing: A CRISPR-Cas9 review.
Mediterr J Med Med Sci. 2026; 2(2): 96-108. [Article number: 37]. https://doi.org/10.5281/zenodo.000000

Keywords: Autism spectrum disorder, bioethics, CRISPR-Cas9, gene therapy, genome editing, neurodiversity

Abstract: Autism spectrum disorder (ASD) is a clinically and biologically heterogeneous group of neuro-developmental conditions characterized by differences in social communication and interaction, restricted interests, repetitive behaviors, and variable patterns of sensory processing. Genetic studies have established ASD as one of the most heritable neurodevelopmental conditions. Still, its architecture ranges from rare, highly penetrant monogenic disorders to a broadly polygenic background shaped by thousands of common variants. The development of clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR-Cas9) has transformed autism research by enabling rapid, programmable, and scalable interrogation of ASD-associated genes in cellular, organoid, and animal systems. This review synthesizes current CRISPR-Cas9 applications in ASD research, focusing on disease modelling, gene function, next-generation editing technologies, delivery to the central nervous system, safety, clinical translation, and ethics. CRISPR has accelerated the modelling of high-confidence ASD-associated genes, including *SHANK3*, *MECP2*, *FMR1*, *CHD8*, *CNTNAP2*, *SCN2A*, and *MEF2C*. Recent advances in base editing, prime editing, CRISPR activation, and epigenome editing offer more precise approaches for specific monogenic neurodevelopmental disorders. However, the translation of genome editing into ASD therapy remains constrained by technical barriers, including delivery across the blood-brain barrier, off-target editing, structural rearrangements, mosaicism, immune responses, and developmental timing. More fundamentally, attempts to edit "autism" as a trait raise profound ethical concerns, particularly from neurodiversity and disability-rights perspectives. We argue that the most defensible clinical horizon for CRISPR in this field is not the elimination of autism, but carefully governed somatic intervention for severe, medically disabling features of specific monogenic syndromes, pursued in partnership with autistic people, families, clinicians, and disability communities.

Introduction

Autism spectrum disorder (ASD) describes a heterogeneous group of neurodevelopmental conditions characterized by persistent differences in social communication and interaction, together with restricted, repetitive patterns of behavior, interests, or activities [1]. Current surveillance estimates indicate that ASD identification has increased substantially over recent decades, with the United States Autism and Developmental Disabilities Monitoring Network reporting a prevalence of about 1 in 31 among 8-year-old children in 2022 [2]. This rise

reflects multiple factors, including broadened diagnostic criteria, increased awareness, improved access to evaluation, and changes in ascertainment practices rather than a single biological cause . ASD is among the most heritable neurodevelopmental conditions. Twin and family studies estimate high heritability, with concordance rates substantially higher in monozygotic than dizygotic twins [3, 4]. Genomic studies have shown that ASD risk arises from a continuum of genetic variation. At one end are rare, highly penetrant mutations in genes such as *SHANK3*, *MECP2*, *FMR1*, *CHD8*, *SCN2A*, and *CNTNAP2*. At the other end is a polygenic background involving thousands of common variants of small effect [5, 6]. This genetic complexity has important implications for gene editing: while specific monogenic syndromes may be biologically plausible targets for gene-based intervention, idiopathic or polygenic ASD is not realistically addressable by editing a single locus. CRISPR-Cas9 has revolutionized functional genomics and disease modelling. By using a guide RNA to direct Cas9 nuclease to a genomic target, researchers can introduce site-specific double-strand breaks that are repaired by endogenous DNA repair pathways [7, 8]. Since its adaptation as a genome engineering platform, CRISPR-Cas9 has enabled the rapid generation of animal models, isogenic induced pluripotent stem cell models, and human brain organoids for ASD-associated genes [9, 10]. Recently, base editing, prime editing, CRISPR activation, CRISPR interference, and epigenome editing have expanded the field beyond double-strand-break-mediated editing. This review provides an updated synthesis of CRISPR-Cas9 applications in autism research as of June 2026. It emphasizes four themes: First, CRISPR as a research tool for modelling ASD-associated genes; second, next-generation editing technologies relevant to monogenic neurodevelopmental disorders; third, delivery and safety challenges in the central nervous system; and fourth, ethical considerations, particularly those raised by autistic self-advocates and disability scholars.

Genetic architecture of ASD and implications for gene editing

Rare and common genetic variation: Large-scale genomic studies have demonstrated that ASD risk involves rare and common variation. Exome sequencing has identified numerous high-confidence ASD-associated genes, many of which are involved in chromatin regulation, transcriptional control, synaptic function, neuronal excitability, and protein translation [5]. A major exome sequencing study implicated developmental and functional mechanisms in ASD biology, identifying risk genes involved in early neurodevelopment and mature neuronal function [5]. Recent analyses integrating de novo and inherited variants across more than 42,000 ASD cases identified additional moderate-risk genes and reinforced the view that ASD genetic architecture includes rare high-impact variants and inherited background variation [6]. This architecture determines where CRISPR may be useful. For rare monogenic or syndromic forms, editing or gene modulation may theoretically address a causative molecular lesion. For most idiopathic ASD, however, no single mutation explains the phenotype. Editing a single locus in polygenic ASD would therefore be scientifically implausible and ethically problematic.

Convergent biological pathways: Despite genetic heterogeneity, ASD-associated genes converge on several biological pathways. These include synapse formation and plasticity, chromatin remodeling, transcriptional regulation, neuronal excitability, and translational control [11, 12]. Databases such as SFARI Gene have helped organize ASD-associated genes according to evidence strength and biological function [13]. This convergence has made CRISPR particularly valuable as a functional tool: Rather than treating ASD as a single entity, researchers can use CRISPR to interrogate specific pathways and cellular phenotypes associated with defined genetic variants.

Syndromic versus idiopathic ASD: CRISPR-based therapeutic strategies are most plausible for syndromic, monogenic neurodevelopmental disorders in which a defined molecular lesion contributes substantially to morbidity. Conditions such as Rett syndrome, fragile X syndrome, Phelan-McDermid syndrome, Angelman syndrome, and some *SCN2A*- or *MEF2C*-related neurodevelopmental disorders may include autistic traits but

also involve seizures, motor dysfunction, intellectual disability, regression, sleep disturbance, feeding difficulties, or other medical complications. These conditions are more plausible candidates for gene-based therapies than idiopathic ASD because they involve identifiable molecular mechanisms. This distinction is ethically important. The goal of therapeutic intervention in severe syndromic conditions should be framed as alleviating suffering, improving communication, reducing seizures, restoring physiological gene dosage, or preventing life-threatening complications, not eliminating autistic identity or neurodivergent traits.

Gene architecture of high-priority ASD-associated targets: A precise discussion of CRISPR feasibility in ASD requires attention not only to gene function but also to gene architecture, dosage sensitivity, mutational mechanism, and cell-type expression. Genes associated with syndromic ASD differ substantially in their suitability for editing. Haplo-insufficient genes such as *SHANK3*, *SCN2A*, *CHD8*, and *MEF2C* may be amenable to gene replacement, CRISPR activation, or mutation-specific correction, whereas genes with toxic gain-of-function or dosage-sensitive effects require more cautious strategies [5, 6].

Figure 1: Genetic architecture of ASD and relevance to CRISPR-based intervention

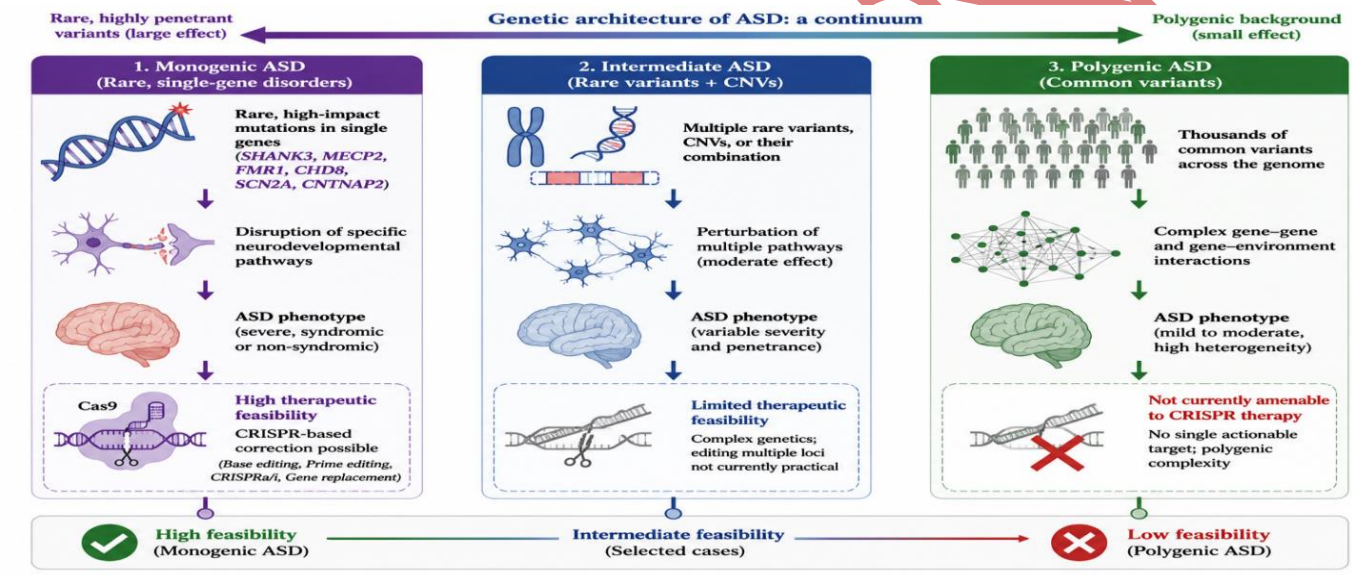


Figure 2: Gene structure and therapeutic logic for major ASD-associated genes

Gene (ASD relevance)	Gene structure (exons and isoforms)	Major mutation types in ASD	Protein domains (key functions)	Therapeutic logic (editing / modulation)	Editing strategy suitability
SHANK3 (Synaptic scaffolding, neurodevelopment)	5′ 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 3′ — Multiple isoforms via alternative splicing	• Loss-of-function (nonsense, frameshift, splice-site) • Large deletions / CNVs	ANK – SH3 – PDZ – PRO — Scaffolding of synaptic complexes	Loss-of-function due to haploinsufficiency; potential for restoration or replacement	**High** (CRISPRa, gene replacement, exon correction)
MECP2 (Dosage-sensitive, synaptic regulation)	5′ 1 2 3 4 3′ — Single major isoform (complex regulation)	• Missense • Nonsense / frameshift • Duplications (causing overexpression)	MBD – TRD – CTD — DNA binding, transcriptional regulation	Both loss and gain of function; requires precise and tightly regulated approaches	**Moderate** (Base editing, prime editing, CRISPRi/a with tight control)
FMR1 (Fragile X, translation regulation)	5′ 5′ UTR – CGG Repeat – Coding 3′ — Single major isoform; repeat expansion in 5′ UTR	• CGG repeat expansion • Hypermethylation of promoter • Silencing of gene	KH1 – KH2 – RGG — RNA binding, translational control	Epigenetically silenced; reactivation of expression is therapeutic goal	**High** (CRISPRa, epigenome editing / demethylation)
CHD8 (Chromatin remodeling, neurodevelopment)	5′ 1 2 3 4 5 6 7 8 … 38 3′ — Multiple isoforms via alternative splicing	• Loss-of-function (nonsense, frameshift) • Missense • Deletions / CNVs	PHD – CHD – Helicase – DNA binding — Chromatin remodeling and transcriptional regulation	Haploinsufficiency; restoration of normal expression or function	**High** (CRISPRa, gene replacement, exon correction)
SCN2A (Neuronal excitability, ion channel function)	5′ 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 3′ — Multiple isoforms via alternative splicing	• Missense (gain or loss) • Nonsense / frameshift • Splice-site variants	DI – DII – DIII – DIV — Voltage-gated sodium channel (ion conduction)	Gain or loss of function depending on mutation; requires precise modulation	**Moderate** (Base editing, prime editing, CRISPR modulation)

Table 1: Gene structure and therapeutic relevance of major ASD-associated genes

Gene	Chromosomal locus	Key protein domains	Main protein function	Disease association	Pathogenic mechanism	Editing/ therapeutic relevance
SHANK3	22q13.33	Ankyrin repeats; SH3; PDZ; proline-rich region; SAM domain	Postsynaptic density scaffolding; glutamatergic synapse organization	Phelan-McDermid syndrome; syndromic ASD	Haploinsufficiency; deletions; truncating variants	Gene replacement, CRISPRa, or mutation correction is plausible; isoform complexity is a challenge [14, 15]
MECP2	Xq28	Methyl-CpG-binding domain; transcriptional repression domain	Chromatin regulation and transcriptional modulation	Rett syndrome; MECP2 duplication syndrome	Loss-of-function (Rett); overexpression (duplication syndrome)	Requires tightly regulated expression; epigenome editing or regulated gene therapy preferred [16, 17]
FMR1	Xq27.3	5′ UTR CGG-repeat region; KH domains; RGG box; encodes FMRP	RNA-binding protein regulating synaptic translation	Fragile X syndrome	CGG-repeat expansion; methylation; transcriptional silencing	Epigenome editing or demethylation-based reactivation may restore endogenous expression [18]
CHD8	14q11.2	ATPase/helicase domains; chromodomains; SANT domain	Chromatin remodelling; transcriptional regulation of broad gene networks	CHD8-related neurodevelopmental disorder; ASD with macrocephaly	Haploinsufficiency	CRISPR modelling and CRISPRa-based dosage rescue are active research strategies [19,20]
CNTNAP2	7q35-q36.1	Large neurexin-family transmembrane protein; EGF-like domains; laminin-G domains	Neuronal connectivity; cortical circuit development	CNTNAP2-associated neurodevelopmental disorder; ASD; epilepsy	Biallelic loss-of-function; rare deleterious variants	CRISPR correction partially rescued organoid overgrowth phenotypes [21]
SCN2A	2q24.3	27 exons; voltage-gated sodium channel Nav1.2; four homologous transmembrane domains DI–DIV	Neuronal excitability, particularly in excitatory cortical neurons	SCN2A-related epilepsy; developmental delay; ASD	Gain-of-function or loss-of-function, depending on the variant	ASO downregulation for gain-of-function variants; CRISPRa or gene replacement for loss-of-function [22]
MEF2C	5q14.3	MADS-box domain; MEF2 domain; transactivation domain	Activity-dependent transcription; synapse development	MEF2C haploinsufficiency syndrome; ASD features	Haploinsufficiency; pathogenic missense variants	In vivo base editing reversed behavioural phenotypes in *Mef2c*-mutant mice [23]
UBE3A	15q11-q13	HECT ubiquitin ligase domain	E3 ubiquitin ligase; protein degradation	Angelman syndrome; ASD features	Loss of maternal allele; paternal allele silenced by *UBE3A-ATS*	ASO-mediated paternal allele unsilencing is clinically advanced; CRISPR approaches remain preclinical [24]

ASD: autism spectrum disorder; CRISPRa: CRISPR activation; ASO: antisense oligonucleotide; FMRP: fragile X mental retardation protein; UTR: untranslated region

CRISPR-Cas9 as a tool for ASD modelling

Animal models: Before CRISPR, engineering animal models was slow and technically demanding. CRISPR-Cas9 enabled efficient generation of knockout, knock-in, and conditional models across multiple species. ASD-relevant models have been generated in mice, rats, zebrafish, macaques, and dogs [9, 10]. *SHANK3* is one of the most extensively modelled ASD-associated genes. *SHANK3* encodes a postsynaptic scaffolding protein, and haploinsufficiency causes Phelan-McDermid syndrome, a syndromic neurodevelopmental disorder frequently associated with autistic features [14]. Restoration experiments in mice have shown that re-expression of *Shank3*

can rescue selected synaptic and behavioural phenotypes, suggesting that some neurodevelopmental phenotypes remain modifiable after early development [25, 26]. Early restoration appears to produce broader rescue than adult restoration, highlighting the importance of developmental timing [25]. CRISPR has also enabled non-human primate and canine models. *SHANK3*-mutant macaques generated using CRISPR-Cas9 displayed altered social behavior, repetitive behaviors, sleep disturbance, and changes in brain connectivity [27]. More recently, CRISPR-mediated *SHANK3* disruption in beagle dogs produced ASD-relevant behavioural and neurodevelopmental phenotypes, expanding comparative models beyond rodents and primates [28].

Human cellular and organoid models: Human induced pluripotent stem cells and cerebral organoids provide a complementary platform for modelling ASD-associated variants in human genetic backgrounds. CRISPR allows the creation of isogenic lines in which the edited and control cells differ only at the target locus. This design reduces confounding by genetic background and strengthens causal inference. Recent organoid studies demonstrate the power of CRISPR-based modelling. *CHD8* haploinsufficiency in human cerebral organoids disrupts excitatory and inhibitory neuronal trajectories, providing a model of altered neurodevelopmental timing [19]. *CNTNAP2*-associated ASD has been modelled in forebrain organoids, where patient-derived organoids showed cortical overgrowth and altered progenitor proliferation; CRISPR correction partially rescued the phenotype [21]. High-throughput CRISPR-organoid-single-cell RNA sequencing systems have further enabled pooled screening of dozens of ASD-associated genes in human brain organoids, identifying vulnerable developmental cell states and gene regulatory networks [20].

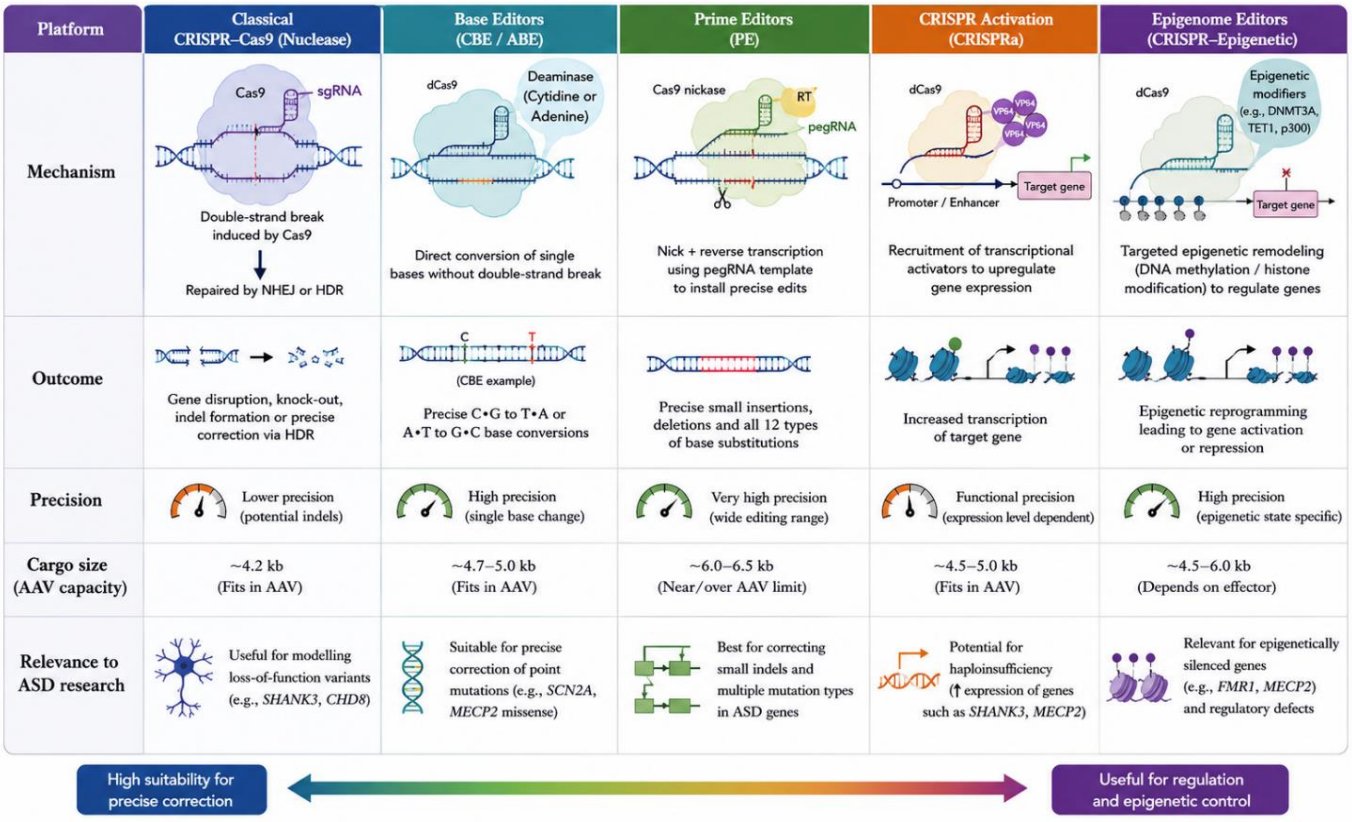
Next-generation genome and epigenome editing: Classical CRISPR-Cas9 relies on double-strand DNA breaks. Although powerful, this approach can produce unintended insertions, deletions, chromosomal rearrangements, and large structural variants [29]. These risks are particularly important in neurons, which are largely post-mitotic and difficult to replace. Newer editing systems seek to improve precision and reduce dependence on double-strand breaks.

Table 2: Genome and epigenome editing platforms relevant to ASD research

Editing platform	Molecular mechanism	ASD-Relevant application	Key advantage	Major limitation
CRISPR-Cas9 nuclease	Double-strand break followed by NHEJ or HDR	Knockout/knock-in models; gene disruption	Efficient, programmable, widely validated	Indels; off-target cuts; structural variants [29, 30]
Base editing	Deaminase fused to Cas9 Nickase or dead Cas9	Correction of single-nucleotide pathogenic variants	Avoids double-strand breaks; high precision	Limited edit types; bystander edits; PAM constraints [31]
Prime editing	Cas9 nickase fused to reverse transcriptase, guided by pegRNA	Precise correction of substitutions, small insertions, and deletions	Flexible; does not require double-strand breaks or donor DNA	Large cargo size; delivery to CNS is challenging [32, 33]
CRISPR activation (CRISPRa)	dCas9 fused to a transcriptional activator	Dosage rescue in haploinsufficiency: gene upregulation	Does not alter the DNA sequence	Requires durable, cell-specific, and titratable regulation
CRISPR interference (CRISPRi)	dCas9 fused to transcriptional repressor	Downregulation of gain-of-function or overexpressed genes	Reversible; sequence-preserving	Persistence and specificity uncertain
Epigenome editing	dCas9 fused to methylation/demethylation or chromatin-modifying effectors	*FMR1* reactivation; *MECP2* dosage modulation	Preserves DNA sequence; targets epigenetic mechanism	Persistence, specificity, and long-term safety remain uncertain [18, 34]

NHEJ: non-homologous end joining; HDR: homology-directed repair; pegRNA: prime editing guide RNA; dCas9: catalytically dead Cas9; PAM: protospacer adjacent motif; CNS: central nervous system

Figure 3: CRISPR-Cas9 and next-generation editing platforms in ASD research



Base editing: Base editing enables direct conversion of one nucleotide to another without generating a double-strand break [31]. This is particularly relevant for monogenic neurodevelopmental disorders caused by pathogenic point mutations. In a recent ASD-relevant study, whole-brain in vivo base editing corrected an ASD-associated *Mef2c* mutation in mice, restored MEF2C protein expression, and reversed behavioural abnormalities [23]. Although this work remains preclinical, it represents a major proof of principle for correcting single-base neurodevelopmental mutations in the brain.

Prime editing: Prime editing expands the editable range by coupling a Cas9 nickase to a reverse transcriptase guided by a prime-editing guide RNA [32]. In 2025, in vivo prime editing was shown to rescue alternating hemiplegia of childhood in mouse models by correcting *ATP1A3* mutations in the central nervous system [33]. Although alternating hemiplegia is not ASD, the study is highly relevant because it demonstrates that prime editing can correct pathogenic variants in the brain and improve neurological phenotypes in vivo.

Epigenome editing and gene reactivation: Epigenome editing may be particularly useful where the underlying gene sequence is intact but transcriptionally silenced. Fragile X syndrome is caused most often by CGG-repeat expansion and methylation-mediated silencing of *FMR1*. CRISPR-based DNA methylation editing has reactivated *FMR1* and rescued electrophysiological abnormalities in patient-derived neurons [18]. Rett syndrome provides another compelling example. Because females with Rett syndrome often carry one mutant and one wild-type *MECP2* allele, reactivation of the healthy allele on the inactive X chromosome is a potential therapeutic strategy. Recent work using multiplex epigenome editing reactivated *MECP2* from the inactive X chromosome in Rett syndrome neurons and rescued cellular phenotypes [34]. However, *MECP2* is highly dosage-sensitive, and deficiency and duplication are pathogenic. Any therapeutic strategy must therefore achieve precise, cell-specific, and physiologically appropriate expression.

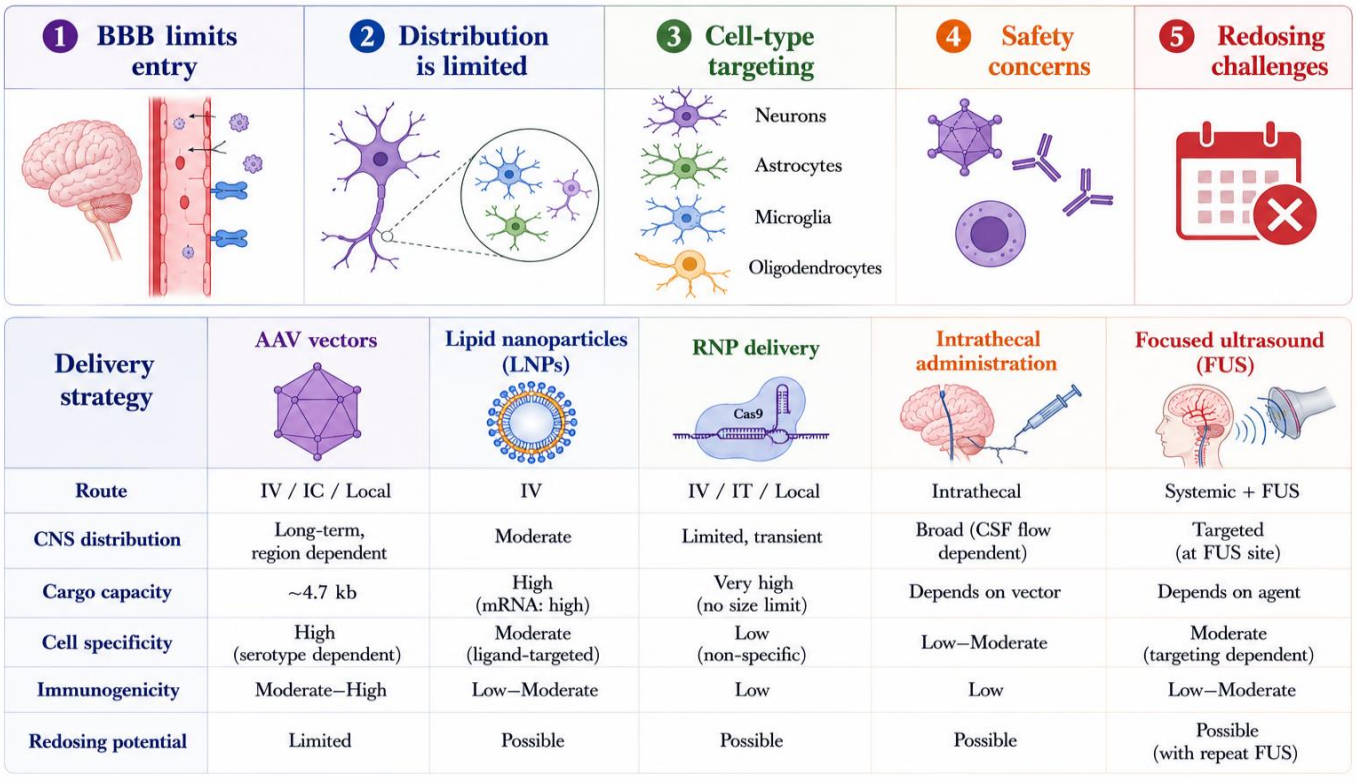
Delivery to the central nervous system: Delivery remains one of the greatest obstacles to clinical genome editing for neurodevelopmental disorders. Editing machinery must reach the appropriate brain regions, cell types, and developmental windows while minimizing immune responses, off-target tissue exposure, and toxicity.

Table 3: Delivery strategies for CRISPR-based editing to the central nervous system

Delivery platform	Mechanism	ASD/CNS-relevant example	Advantages	Limitations
Adeno-associated virus (AAV)	Recombinant viral capsid with neuronal tropism; long-term transduction of post-mitotic neurons	Standard platform for CNS gene therapy trials	Established safety profile; long-term expression; multiple serotypes with distinct tropism [35, 36]	Limited cargo capacity (~4.7 kb); pre-existing and induced immunity; limited redosing; uneven CNS distribution
Lipid nanoparticles (LNPs)	Lipid-based nanoparticle encapsulating mRNA or RNP	Emerging CNS delivery; intrathecal routes under investigation	No viral immunogenicity; transient expression; scalable	Limited CNS penetration after systemic administration; endosomal escape challenges
CRISPR-Gold (nanoparticle)	Gold nanoparticle conjugated to Cas9 RNP	Rescued repetitive behaviours in the fragile X mouse model via intracranial injection [37]	Avoids viral immunogenicity; delivers RNP directly	Local delivery only; not yet scalable to the whole brain
Focused ultrasound + BBB opening	Transient, reversible opening of the BBB using microbubbles and ultrasound	Enhanced CRISPR delivery to the brain in preclinical systems [38]	Non-invasive; regionally targeted; reversible	Limited spatial precision; requires specialised equipment; safety in developing brain unclear
Intrathecal/ intracerebroventricular injection	Direct CSF administration	Clinical route for ASO therapies; emerging for gene therapy	Bypasses BBB; broad CNS distribution	Invasive; requires repeat dosing for non-integrating vectors; distribution varies by agent

BBB: blood-brain barrier; RNP: ribonucleoprotein; CSF: cerebrospinal fluid; ASO: antisense oligonucleotide

Figure 4: CNS delivery barriers for CRISPR-based neurodevelopmental therapies



Viral vectors: Adeno-associated virus (AAV) remains the leading delivery platform for central nervous system gene therapy because of its neuronal tropism, relatively favorable safety profile, and capacity for long-term expression [35, 36]. But AAV has important limitations: restricted cargo capacity constraining the packaging of large Cas9 proteins together with guide RNAs and regulatory elements; pre-existing and treatment-induced immunity that can limit efficacy and preclude redosing; and variable distribution across the human brain [35, 36].

Non-viral and physical delivery strategies: Non-viral delivery offers an alternative that avoids some cargo and immunogenicity constraints of viral vectors. CRISPR-Gold, a gold-nanoparticle-based vehicle, delivered Cas9 ribonucleoprotein directly into the mouse brain and rescued exaggerated repetitive behaviors in a fragile X mouse model by editing genes in the mGluR5 pathway [37]. Physical methods to enhance delivery are also advancing; focused ultrasound can transiently and reversibly open the blood-brain barrier to improve the efficiency of CRISPR-based editing in the brain [38].

Safety considerations and clinical translation

Off-target editing and structural variation: Off-target editing remains a central safety concern [39, 40]. Cas9 can cut genomic sites with sequence similarity to the intended target, potentially disrupting genes or regulatory elements [39]. Of growing concern is the recognition that CRISPR-Cas9 can also induce large structural variants, including sizeable deletions, duplications, inversions, and complex rearrangements, at off-target and on-target sites [29, 30]. In the context of editing the developing or mature brain, where neurons are largely post-mitotic and irreplaceable, such unintended changes carry particular weight.

Mosaicism and incomplete editing: When editing is performed in vivo, it frequently affects only a subset of cells, producing a mosaic in which edited and unedited cells coexist [39]. For a polygenic, developmentally distributed condition, partial editing of one locus would be unlikely to produce a coherent therapeutic effect and could introduce unpredictable cellular heterogeneity. For specific monogenic disorders, mosaic correction may provide partial benefit, but the degree of correction required for clinical improvement is not yet established for most ASD-associated syndromes.

Lessons from approved CRISPR therapies: The first regulatory approvals of CRISPR-based therapies for sickle cell disease and transfusion-dependent β-thalassaemia represent a landmark for genome editing [41-43]. However, these therapies are ex vivo haematopoietic stem cell interventions, allowing edited cells to be screened before reinfusion. CNS genome editing is far more complex because cells are edited in vivo, delivery is difficult, and edited neurons cannot be removed or replaced if adverse effects occur.

Clinical trial landscape for ASD-associated syndromes: As of June 2026, there are no approved CRISPR-based therapies for ASD or ASD-associated monogenic neurodevelopmental disorders. Still, several molecular therapies are in clinical development for syndromic neurodevelopmental disorders that frequently include autistic features.

Rett syndrome clinical advances: Rett syndrome currently has the most advanced clinical therapeutic landscape among ASD-associated monogenic syndromes. Trofinetide demonstrated efficacy in a phase 3 randomized controlled trial and became the first pharmacological therapy approved specifically for Rett syndrome in the United States [44]. Gene therapy trials for Rett syndrome are now evaluating regulated or dose-controlled MECP2 replacement strategies, reflecting the critical need to avoid underexpression and overexpression of MECP2.

Angelman syndrome and RNA-targeted therapies: Angelman syndrome provides a compelling example of translating molecular mechanisms into clinical interventions. Because the paternal *UBE3A* allele is epigenetically silenced in neurons by the antisense transcript *UBE3A-ATS*, antisense oligonucleotides designed to block *UBE3A-*

ATS and thereby unsilence the paternal *UBE3A* allele have entered clinical trials [24]. Multiple phase 3 programs are now underway, illustrating the rapid emergence of RNA-based therapies in monogenic neurodevelopmental disease.

Table 4: Clinical trial landscape for ASD-associated monogenic neurodevelopmental disorders

Disorder	Target Gene/ Pathway	Intervention	Modality	Trial ID	Phase	Route	Population	Relevance to CRISPR-ASD Field
Rett syndrome	*MECP2*	Trofinetide	Small-molecule neuropeptide analogue	NCT04181723	Phase 3 (completed; approved)	Oral	Girls and women with Rett syndrome	The first approved disease-targeted therapy informs endpoint design [44]
Rett syndrome	*MECP2*	NGN-401	Regulated AAV gene therapy	NCT05898620	Phase 1/2 (enrolling)	Intrathecal/ intracerebral CNS-directed	Females with typical Rett syndrome	Tests regulated MECP2 replacement; directly relevant to dosage-control challenges
Rett syndrome	*MECP2*	TSHA-102	AAV9 gene transfer with miRNA-responsive regulation	NCT05606614	Phase 1/2 and pivotal development (enrolling)	Intrathecal	Females with Rett syndrome	Demonstrates clinical movement toward regulated CNS gene therapy
Angelman syndrome	*UBE3A-ATS* / paternal *UBE3A*	Rugonersen (RO7248824)	Antisense oligonucleotide	NCT04428281	Phase 1 (completed)	Intrathecal	Children with Angelman syndrome	Proof of clinical feasibility for paternal allele unsilencing [24]
Angelman syndrome	*UBE3A-ATS*	GTX-102 / apazunersen	Antisense oligonucleotide	NCT06617429	Phase 3 (enrolling)	Intrathecal	Children/ Adolescents with deletion Angelman syndrome	Phase 3 programme testing disease-modifying ASO approach
Angelman syndrome	*UBE3A-ATS*	ION582	Antisense oligonucleotide	NCT06914609	Phase 3 (enrolling)	Intrathecal	Children and adults with Angelman syndrome	Additional pivotal ASO programme
Phelan-McDermid syndrome	*SHANK3*	RB001 / JAG201-type programme	AAV-based gene therapy	NCT07014020	Phase 1/2 (enrolling)	CNS-directed	Children with *SHANK3*-related PMS	First-in-human *SHANK3*-related gene therapy trial; directly relevant to monogenic ASD therapy
SCN2A-DEE	*SCN2A* gain-of-function	PRAX-222 / elsunersen	Antisense oligonucleotide	NCT05737784	Phase 1/2 (enrolling)	Intrathecal	Children with early-onset *SCN2A*-DEE	Variant-mechanism-specific precision therapy; relevant to ASD-associated ion-channel genes [22]

NCT identifiers are trial-registry identifiers. DEE: developmental and epileptic encephalopathy; PMS: Phelan-McDermid syndrome; ASO: antisense oligonucleotide; AAV: adeno-associated virus; CNS: central nervous system

Ethical, social, and regulatory dimensions

The somatic-germline distinction: Ethical analysis of gene editing pivots on the distinction between somatic editing, which alters the cells of a single individual and is not heritable, and germline editing, which alters embryos, eggs, or sperm such that changes are transmitted to all future generations [45]. The National Academies concluded that heritable human genome editing should not be permitted to proceed to clinical use until safety and efficacy can be established and a broad societal consensus has been developed [45].

Perspectives from the neurodiversity movement: Any discussion of editing genes associated with autism cannot proceed responsibly without centering the perspectives of autistic people themselves [46-48]. The neurodiversity movement reframes autism not solely as a disorder to be eliminated but as a form of human variation deserving of acceptance, accommodation, and civil rights [46, 47]. From this standpoint, the framing of gene editing as a route to curing or preventing autism is regarded by many autistic self-advocates as stigmatizing and potentially eugenic. Recent ethical guidance for autism genomics recommends community engagement, justice-oriented research design, careful consent processes, and attention to how genetic findings may be used socially and clinically [49].

A defensible ethical framework: A defensible ethical position distinguishes clearly between two categories of application: Somatic treatment of severe medical features of specific monogenic syndromes, such as seizures, neurodevelopmental regression, motor dysfunction, or profound communication impairment, may be ethically justifiable under strict oversight and community engagement. Trait-level or germline attempts to prevent autism, as such, raise serious ethical, social, and disability-rights concerns and should not be considered an acceptable clinical goal.

Table 5: Ethical decision framework for gene editing in ASD-associated conditions

Ethical criterion	Ethically more defensible	Ethically more problematic
Target	Specific, severe, medically disabling features of a defined monogenic syndrome	Autistic traits as such; prevention of autism as a neurodevelopmental identity
Editing type	Somatic editing of the treated individual	Germline editing affecting future generations
Consent	Informed consent from the patient, where possible; proxy consent with independent oversight for children	Editing of embryos or future persons who cannot consent
Evidence base	Strong preclinical safety and efficacy data; validated biomarkers; defined clinical endpoints	Insufficient preclinical evidence; no validated endpoints
Community engagement	Autistic people, disability advocates, and families involved in research design and governance from the outset	Autistic and disability communities are excluded from decision-making
Equity	Equitable access framework in place; benefits not restricted to high-income settings	No access framework; risk of exacerbating health inequalities

Future directions: Future research should prioritize precision over breadth. Rather than attempting to develop gene-editing approaches for ASD as a broad diagnostic category, the field should focus on molecularly defined syndromic conditions in which genotype, disease mechanism, and therapeutic target are clearly established. The most promising near-term applications are likely to involve correction or modulation of monogenic disorders with severe medical burden, such as Rett syndrome, Angelman syndrome, Phelan-McDermid syndrome, fragile X syndrome, and selected ion-channel disorders. Base editing and prime editing are likely to become increasingly important for variant-specific correction, particularly in cases where a single pathogenic nucleotide change drives disease. CRISPR activation and epigenome editing may be better suited for haploinsufficiency or transcriptionally silenced genes. However, the major determinant of clinical success will be delivery. Safer, more specific, and regulatable CNS delivery systems are needed before in vivo editing can be responsibly attempted in children. Future trials must also develop better outcome measures. Molecular correction alone is insufficient if it does not

translate into meaningful improvements in communication, motor function, seizure burden, sleep, adaptive behavior, or quality of life. Patient- and family-prioritised endpoints should be incorporated early in trial design. Finally, ethical governance must remain central. Autistic individuals, families, disability advocates, clinicians, and scientists should jointly define acceptable goals, unacceptable uses, and fair access frameworks for emerging gene-editing technologies.

Conclusion: CRISPR-Cas9 has already transformed autism research by enabling precise modelling of ASD-associated genes in animals, human cells, and brain organoids. Its most immediate value lies in mechanistic discovery rather than clinical therapy. Next-generation editing technologies offer genuine promise for selected monogenic neurodevelopmental syndromes, particularly where a defined mutation or dosage defect causes severe medical impairment. However, delivery to the brain, off-target effects, structural variants, immune responses, mosaicism, and developmental timing remain major barriers. Equally important are the ethical constraints: autism should not be framed as a trait to be eliminated. The responsible future of CRISPR in this field lies in carefully governed, somatic, condition-specific interventions aimed at reducing serious disability and improving quality of life, developed in meaningful partnership with autistic people, families, clinicians, scientists, and disability-rights communities.

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Author's contribution: Both authors contributed equally and approved the final version of the manuscript and agreed to be accountable for its contents.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: The authors have considered ethical issues, including plagiarism, informed consent, data fabrication or falsification, and double publication or submission.
Generative AI disclosure: No Generative AI was used in the preparation of this manuscript.