Asian Journal of Pediatric Research

Volume 16, Issue 6, Page 30-48, 2026; Article no.AJPR.161020
ISSN: 2582-2950

The SNRPN Bipartite Imprinting Centre in Region 15q11–q13 and Its Epigenetic Role in the Pursuit of a Cure for Angelman Syndrome

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2026/v16i6549

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://pr.sdiarticle5.com/review-history/161020

Review Article

Received: 25/04/2026
Accepted: 15/06/2026
Published: 04/07/2026

Abstract

Angelman syndrome is a severe neurodevelopmental disorder arising from functional loss of the maternal allele of UBE3A, a gene that sits within a cluster of imprinted loci on the long arm of chromosome 15. Expression across this region is governed by a bipartite imprinting centre associated with the SNRPN gene, made up of two physically separated but functionally interdependent elements: the Prader–Willi syndrome smallest region of deletion overlap and the Angelman syndrome smallest region of deletion overlap. Together these elements establish, in the germline, and maintain, throughout somatic life, the parent-of-origin-specific expression pattern that distinguishes Angelman syndrome from its reciprocal disorder, Prader–Willi syndrome. Because the paternal copy of UBE3A remains structurally intact in most patients with Angelman syndrome, merely silenced by a long non-coding antisense transcript whose own expression is dictated by the imprinting centre, this locus has become the focal point of an unusually concentrated translational effort: rather than replacing a missing gene, contemporary therapeutic strategies aim to reverse an epigenetic mark

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Cite as: *Bittmann, S. (2026). The SNRPN Bipartite Imprinting Centre in Region 15q11–q13 and Its Epigenetic Role in the Pursuit of a Cure for Angelman Syndrome. Asian Journal of Pediatric Research, 16(6), 30–48. https://doi.org/10.9734/ajpr/2026/v16i6549*

and thereby unmask a dormant but functional allele. This review draws together the structural biology of the bipartite imprinting centre, the molecular events that establish and maintain its parent-specific epigenotype, the diagnostic and clinical consequences of its disruption, and the rapidly maturing pipeline of antisense oligonucleotides, small molecules, and genome- or epigenome-editing tools designed to exploit this biology therapeutically. Recent clinical trial data, including electroencephalographic and behavioural endpoints from antisense oligonucleotide programmes, are critically appraised alongside preclinical work on CRISPR-based epigenetic editing of the imprinting centre itself, an approach with the conceptual elegance of intervening at the very switch that imprinting biology depends upon. The review concludes that while no disease-modifying therapy is yet approved, the convergence of detailed mechanistic understanding of the SNRPN bipartite imprinting centre with scalable epigenetic editing technologies represents the most plausible route towards a transformative, rather than purely symptomatic, treatment for Angelman syndrome, while candidly addressing the developmental, safety and translational obstacles that remain.

Keywords: Angelman syndrome; SNRPN; bipartite imprinting centre; genomic imprinting; UBE3A; antisense oligonucleotide; epigenome editing; Prader–Willi syndrome.

1. Introduction

1.1 Genomic Imprinting and the Architecture of Parent-of-origin Gene Expression

Genomic imprinting describes the epigenetic phenomenon by which a subset of mammalian genes is expressed according to parent of origin rather than according to the sequence of the allele itself. Imprinted genes tend to cluster together, and expression within a given cluster is coordinated by a *cis*-acting imprinting control region that acquires a parent-specific mark, usually DNA methylation, during gametogenesis (Barlow & Bartolomei, 2014). That mark is then read out somatically through downstream effects on chromatin structure, transcription factor binding, and the production of regulatory non-coding RNAs, generating a pattern of allele-specific silencing that is heritable across cell divisions yet, in principle, reversible (Bartolomei et al., 2020). Because imprinted loci are functionally haploid with respect to the silenced allele, they are unusually exposed to disease: a single mutational or epigenetic event affecting the active copy can cause a complete loss of gene function, with no compensating contribution from the structurally intact but silent allele. This vulnerability underlies a family of human disorders, collectively termed imprinting disorders, that despite considerable clinical heterogeneity share recurring molecular themes of deletion, uniparental disomy, imprinting centre defects, and multilocus methylation disturbance (Eggermann et al., 2015; Monk et al., 2019). Recent disease-primer synthesis has reinforced that imprinting disorders share recurrent molecular categories, including deletions, uniparental disomy and methylation disturbance, even when their clinical presentations differ substantially (Eggermann et al., 2023).

1.2 The 15q11–q13 Locus: Angelman Syndrome and Prader–Willi Syndrome as Reciprocal Disorders

One of the best-characterised imprinted domains in the human genome spans roughly 4 megabases at chromosome 15q11–q13. The locus contains a cluster of paternally expressed genes, including MKRN3, MAGEL2, NDN and the SNRPN/SNURF transcription unit together with its associated small nucleolar RNA clusters, alongside a single, critically important maternally expressed gene, UBE3A, which encodes an E3 ubiquitin-protein ligase (Bird, 2014). Loss of paternal gene expression across this domain produces Prader–Willi syndrome, marked by neonatal hypotonia, later hyperphagia and obesity, hypogonadism, and a comparatively mild intellectual disability (Cassidy & Driscoll, 2009; Cassidy et al., 2012). Loss of maternal UBE3A expression instead produces Angelman syndrome, a clinically very different disorder characterised by severe intellectual disability, virtual absence of expressive speech, gait ataxia, microcephaly, a high prevalence of epilepsy, and a characteristically happy demeanour with frequent, often unprovoked laughter (Bird, 2014; Williams et al., 2006). That two such different phenotypes emerge from disruption of the same chromosomal segment, depending entirely on which parental allele is affected, has made 15q11–q13 something of a textbook case for the study of genomic imprinting in humans. Its molecular dissection has, in turn, illuminated principles of imprinting biology that extend well beyond this single region (Buiting et al., 2016; Monk et al., 2019).

1.3 The Bipartite Imprinting Centre as the Master Regulatory Switch

Coordinated regulation of paternal and maternal gene expression across 15q11–q13 is achieved by a single, bipartite imprinting centre associated with the SNRPN locus. This is not a contiguous sequence but two physically separated components: a 4.3-kilobase region encompassing the SNRPN promoter and exon 1, generally called the Prader–Willi syndrome smallest region of deletion overlap, and an 880-base-pair element located roughly 35 kilobases upstream, called the Angelman syndrome smallest region of deletion overlap (Buiting et al., 1995; Buiting et al., 1999; Buiting et al., 2001; Färber et al., 1999). The discovery, through the study of rare families with inherited imprinting defects, that deletion of either element could independently disrupt the parent-specific epigenotype of the entire domain established what is now known as the bipartite model of the imprinting centre. It also clarified that the two elements operate in a temporal hierarchy rather than as equal partners. During oogenesis, the Angelman syndrome element acts in *trans*, across the intervening 35 kilobases, to impose a repressive imprint on the Prader–Willi syndrome element on the maternal allele. Once correctly imprinted, that element then functions, on the paternal allele and throughout life, as a bidirectional activator of the paternally expressed gene cluster and, indirectly, as the source of the long non-coding antisense transcript that silences paternal UBE3A in neurons (Lewis et al., 2015). The result is a uniquely consequential arrangement: a single regulatory switch, set once in the germline, determines the lifelong epigenetic fate of an entire multigene domain and, via the UBE3A antisense transcript, the expression of a gene located hundreds of kilobases away. Recent translational work has further strengthened the need to connect this regulatory architecture with trial-readiness measures, because outcome selection and neurophysiological biomarkers must be sensitive enough to detect biologically plausible treatment effects in Angelman syndrome (Tjeertes et al., 2023; Hagenaar et al., 2024).

1.4 Scope and Objectives of this Review

Although the existing literature has separately described imprinting-centre biology, antisense-based unsilencing and clinical trial methodology, a remaining research gap is the limited integration of these mechanistic, endpoint-development and preclinical-translational strands into a single evaluation of how the SNRPN bipartite imprinting centre can be exploited therapeutically (Tjeertes et al., 2023; Hagenaar et al., 2024; Myers et al., 2025).

This review addresses the structural and functional biology of the SNRPN bipartite imprinting centre and critically evaluates its centrality to current efforts to develop a disease-modifying, rather than purely symptomatic, treatment for Angelman syndrome. It moves from fundamental mechanism towards clinical translation. It first describes the architecture and germline establishment of the bipartite imprinting centre and its two constituent elements; it then examines how disruption of this regulatory system produces the principal molecular subtypes of Angelman syndrome, and how those subtypes are diagnosed clinically and in the laboratory; it goes on to survey the major classes of therapeutic strategy that exploit the intact, but epigenetically silenced, paternal UBE3A allele, including small-molecule unsilencers, antisense oligonucleotides, and genome- or epigenome-editing approaches; and it closes with a critical appraisal of the current clinical trial landscape, the biomarkers used to track treatment effect, and the translational and developmental obstacles that still constrain progress towards a cure. Throughout, the review keeps one eye on Prader–Willi syndrome, since several of the most conceptually ambitious strategies under development, particularly those targeting the imprinting centre itself rather than its downstream consequences, are explicitly designed to be applicable, with modification, to both disorders. The aim is not merely descriptive but critical: to assess where the field's mechanistic confidence genuinely supports therapeutic optimism, and where substantial uncertainty remains regarding efficacy, durability, developmental timing and long-term safety.

2. Methods for Literature Selection

This article was prepared as a narrative, rather than systematic, review, a choice that reflects the nature of the underlying question. A narrative format is better suited than a systematic one when the aim is to integrate mechanistic, genetic, clinical and translational literatures spanning several decades and multiple disciplinary traditions into a single coherent critical synthesis, rather than to answer a narrowly defined, quantifiable question amenable to formal risk-of-bias appraisal and meta-analysis. Systematic and narrative reviews serve complementary purposes, and the latter is particularly well suited to deepening conceptual understanding of a heterogeneous evidence base (Greenhalgh et al., 2018). Given how quickly therapeutic development in this field

is moving, a narrative approach also allowed mechanistic studies, clinical trial reports and regulatory milestones from very different study designs to be drawn into a single thematically organised account.

The principal literature search was conducted across PubMed, Web of Science, Scopus and Google Scholar, supplemented by targeted searches of OMIM, ClinicalTrials.gov, the GeneReviews repository, Orphanet, and the Human Gene Mutation Database. These last five resources were used mainly to verify nomenclature, prevalence estimates, and the registration status of ongoing interventional trials, rather than as primary sources of mechanistic evidence. Search terms combined the core concepts "Angelman syndrome", "Prader-Willi syndrome", "SNRPN", "UBE3A", "imprinting centre" or "imprinting center", "UBE3A-ATS", "genomic imprinting", "antisense oligonucleotide", and "epigenome editing" or "CRISPR", combined with Boolean operators into strings such as ("Angelman syndrome" AND "imprinting center") and ("UBE3A-ATS" AND "antisense oligonucleotide"). The search was concentrated on the period from roughly January 2010 to February 2026, reflecting the window during which the therapeutics discussed in this review were developed and tested clinically, while the foundational mechanistic papers that established the structure of the bipartite imprinting centre, dating from the mid-1990s onward, were retained as essential conceptual anchors regardless of publication date — standard practice when reviewing a long-studied genetic locus.

Records were first screened by title and abstract for relevance to the molecular biology, genetics, clinical phenotype or therapeutics of the 15q11–q13 imprinted domain, and full texts were then retrieved for studies judged potentially relevant. Duplicates arising from overlapping database coverage were identified by comparing digital object identifiers, or, where these were unavailable, by comparing author lists, titles and publication years. The search was restricted to English-language publications, reflecting both the dominant language of the relevant primary literature and practical constraints on translation and verification. Conference abstracts, unpublished theses, preprints that had not undergone peer review, patents, and trade or industry publications were excluded; priority was given throughout to original peer-reviewed research articles and to review articles from groups with sustained, internationally recognised programmes of work on imprinting disorders. Influential or field-defining studies were identified through a combination of citation frequency within the retrieved literature, explicit identification as landmark work within subsequent reviews, and their role in establishing concepts — such as the bipartite structure of the imprinting centre, or the feasibility of antisense-mediated unsilencing of paternal UBE3A — that are now treated as foundational. Reference lists of key papers and recent reviews were also hand-searched to capture additional studies missed by the database searches, a snowballing step that proved particularly useful for locating early molecular genetic studies of imprinting centre microdeletions that predate consistent digital indexing.

3. Structural Organisation of the SNRPN Bipartite Imprinting Centre

3.1 Genomic Architecture of the 15q11–q13 Imprinted Domain

The 15q11–q13 imprinted domain spans roughly 4 megabases and contains, besides the SNRPN/SNURF transcription unit itself, a cluster of paternally expressed protein-coding genes (MKRN3, MAGEL2, NDN), a large series of small nucleolar RNA genes embedded within the long paternally expressed SNHG14 transcript (including the SNORD116 and SNORD115 clusters), and the maternally expressed UBE3A gene towards the distal end of the cluster (Bird, 2014; Buiting et al., 2016). Unlike many other imprinted domains, where several genes each carry their own independent differentially methylated region, the whole of 15q11–q13 is governed by a single regulatory unit: the bipartite imprinting centre associated with SNRPN. This means that mutational or epigenetic disruption of the imprinting centre has consequences across the entire domain, a feature that both explains the contiguous-gene character of Prader–Willi syndrome and helps account for the comparatively restricted molecular basis of Angelman syndrome, where only one gene, UBE3A, is rendered functionally haploinsufficient by imprinting centre dysfunction (Buiting et al., 2016).

3.2 The Prader–Willi Syndrome Smallest Region of Deletion Overlap

The Prader–Willi syndrome element of the bipartite imprinting centre, usually abbreviated PWS-IC or PWS-SRO, is a 4.3-kilobase sequence covering the SNRPN promoter and first exon (Buiting et al., 1998). On the paternal allele this region is unmethylated and acts, together with downstream regulatory architecture, as a bidirectional activator that drives transcription of the upstream paternally expressed genes, including NDN, as well as of the long SNHG14/SNURF-SNRPN transcript itself (Lewis et al., 2015). Crucially for the

pathogenesis of Angelman syndrome, this same transcriptional activity at the unmethylated paternal PWS-IC also drives production of the antisense transcript that runs through, and silences, the paternal copy of UBE3A in neurons. On the maternal allele, by contrast, the PWS-IC is densely methylated — a mark laid down during oogenesis under the direction of the second element of the bipartite centre — and this methylation silences the maternal SNRPN promoter. That, in turn, prevents both paternal-pattern gene activation and, crucially, production of the antisense transcript that would otherwise silence maternal UBE3A as well; the maternal UBE3A allele therefore remains free to be expressed (Färber et al., 1999).

3.3 The Angelman Syndrome Smallest Region of Deletion Overlap

The second element of the bipartite imprinting centre, the AS-IC or AS-SRO, is an 880-base-pair sequence located roughly 35 kilobases upstream of the PWS-IC, and contains one of several alternative upstream exons of the SNURF-SNRPN transcription unit (Buiting et al., 1999; Färber et al., 1999). Functional work, including analysis of human oocyte transcripts, indicates that the AS-IC serves as the principal transcription start site for SNRPN-derived transcripts during oogenesis, and that transcription beginning at the AS-IC and reading through the downstream PWS-IC is mechanistically required for the de novo establishment of maternal-pattern methylation at the latter (Lewis et al., 2015). The AS-IC does not, in other words, become methylated itself in order to pass on the maternal imprint; rather, it acts in *trans*, through the act of transcribing across the intervening genomic distance, to impose methylation and consequent silencing upon the PWS-IC on the maternal allele. Deletion of the AS-IC — even though it lies outside the PWS-IC sequence conventionally interrogated by clinical methylation assays — abolishes this transcriptional imprint-setting activity. The result is a paternal-pattern, unmethylated PWS-IC inherited on the maternal chromosome, with consequent failure of maternal UBE3A expression and a clinical picture of Angelman syndrome despite the chromosome being maternally derived (Buiting et al., 1999; Buiting et al., 2001).

3.4 The Functional Interaction between the Two Elements: An Imprint-Switch Model

The relationship between the two halves of the bipartite imprinting centre is therefore sequential rather than simultaneous, and hierarchical rather than symmetrical — a pattern that has come to be known as an imprint-switch model. During oogenesis, transcriptional activity originating at the AS-IC and passing through the PWS-IC establishes maternal-pattern methylation and silencing at the latter; this mark is then maintained, largely independently of any further AS-IC activity, through pre- and post-implantation development and into adult somatic tissue (Lewis et al., 2015). On the paternal allele, by contrast, no AS-IC-driven transcription occurs during spermatogenesis, so the PWS-IC never acquires methylation and consequently retains, for life, its ability to act as a transcriptional activator of the paternally expressed gene cluster — including the long antisense transcript responsible for silencing paternal UBE3A in neurons. This model neatly explains why deletions of the AS-IC and the PWS-IC, despite sitting tens of kilobases apart, converge on the same disease phenotype when affecting the appropriate parental chromosome. It also makes clear that the imprinting centre is best understood not as two independent regulatory elements but as a single, spatially distributed switch whose two halves perform temporally distinct jobs: the AS-IC sets the imprint in the oocyte, while the PWS-IC reads it out, or fails to, in somatic cells thereafter. Work examining common, non-pathogenic sequence variation within the AS-IC has further reinforced the importance of this element: a haplotype carrying a small deletion that removes a binding site for the transcription factor SOX2 is associated with a measurably increased risk of maternal imprinting defects, providing genetic evidence — independent of rare pathogenic deletions — that the precise sequence architecture of the AS-IC contributes quantitatively to the fidelity of imprint establishment (Beygo et al., 2020).

As Table 1 makes clear, the two elements of the bipartite centre differ markedly in size, in the developmental window during which they exert their main effect, and in which parental allele their activity matters most for, yet neither works on its own: one element alone is never sufficient to establish a normal imprint, and pathogenic deletion of either is sufficient to abolish it.

4. Establishment and Maintenance of the Imprint: Molecular Mechanisms

4.1 Germline Establishment of the Maternal Imprint

Establishment of the maternal-pattern epigenotype at the PWS-IC occurs during oogenesis and depends on transcriptional readthrough originating at the AS-IC. Analysis of human oocyte RNA shows that transcripts

beginning at the AS-IC use alternative splice donor sites to cross the PWS-IC region before splicing into the body of the SNRPN transcript. This pattern of transcriptional transit across the PWS-IC is thought to recruit the DNA methylation machinery to the locus, converting an initially unmarked chromosomal region into one bearing a stable, heritable maternal methylation mark (Lewis et al., 2015). This fits with broader principles of genomic imprinting, in which transcription itself, rather than sequence recognition alone, is frequently the proximate trigger for de novo methylation at imprinting control regions during gametogenesis (Barlow & Bartolomei, 2014). It is worth noting that the mouse genome lacks a sequence directly homologous to the human AS-SRO; the murine locus instead relies on a series of repeated upstream promoters to achieve an analogous transit effect. The broad principle of transcription-dependent imprint establishment therefore appears conserved across species even though the precise sequence architecture implementing it has diverged — a point of some practical relevance when interpreting murine preclinical models discussed later in this review.

Table 1. Comparative structural and functional features of the two elements of the SNRPN bipartite imprinting centre

Feature	PWS-IC (PWS-SRO)	AS-IC (AS-SRO)
Approximate size	4.3 kilobases	880 base pairs
Location relative to SNRPN	Encompasses SNRPN promoter and exon 1	~35 kb upstream of PWS-IC
Developmental timing of action	Read out somatically, throughout life	Acts during oogenesis only
Allele on which it is active	Paternal (unmethylated, transcriptionally active)	Maternal (drives transcription that imprints PWS-IC)
Principal molecular function	Bidirectional promoter/activator of paternal gene cluster and UBE3A-ATS	Source of imprint-setting transcription across PWS-IC in oocytes
Consequence of deletion	Failure to establish/maintain paternal imprint → Prader–Willi syndrome	Failure to establish maternal imprint → Angelman syndrome
Common variation effect	Less well characterised	SOX2-binding-site variant haplotype associated with increased imprinting-defect risk

Sources: Buiting et al. (1995); Buiting et al. (1999); Buiting et al. (2001); Färber et al. (1999); Lewis et al. (2015); Beygo et al. (2020)

4.2 DNA Methylation at the SNRPN Promoter and Its Somatic Maintenance

Once established in the oocyte, methylation of the maternal PWS-IC must be faithfully propagated through every subsequent mitotic division of somatic development. This maintenance process relies on the canonical machinery of allele-specific methylation maintenance rather than on continued transcriptional activity at the AS-IC, which is itself a germline-restricted event. This maintained mark is the molecular substrate interrogated by the methylation-sensitive assays — methylation-specific polymerase chain reaction and methylation-sensitive multiplex ligation-dependent probe amplification chief among them — that constitute the first-line laboratory test for both Angelman syndrome and Prader–Willi syndrome, since these assays detect the expected biparental methylation pattern at the SNRPN locus directly, regardless of which underlying molecular mechanism produced the abnormality (Buiting et al., 2016; Williams et al., 2010). The somatic stability of this mark also explains why imprinting defects, once established, produce a uniform and lifelong epigenotype rather than a developmentally variable one, although rare instances of post-zygotic mosaicism for imprinting defects have been documented and remain relevant to recurrence-risk counselling (Duis et al., 2022).

4.3 Transcriptional Antisense Regulation: the UBE3A-ATS Mechanism

The consequence of an unmethylated, paternally imprinted PWS-IC that matters most for Angelman syndrome is the production, specifically within neurons, of a very long antisense non-coding transcript, UBE3A-ATS, which originates within the SNHG14 transcription unit downstream of SNRPN and extends, in antisense orientation, through the UBE3A locus itself (Meng et al., 2015). In neurons, but notably not in most other somatic tissues, expression of this antisense transcript from the paternal allele is sufficient to silence the paternal copy of UBE3A in *cis*, through a mechanism now understood to involve transcriptional collision and interference rather than classical RNA interference or chromatin-based heterochromatin spreading (Vihma et al.,

2024). This tissue specificity matters a great deal, both biologically and clinically: because UBE3A is biallelically expressed in most non-neuronal tissues, loss of the maternal allele in Angelman syndrome produces a neuron-specific functional null state, even though the paternal allele remains structurally entirely normal throughout the body. This single fact — that every neuron in a person with Angelman syndrome carries an intact, functional copy of UBE3A, simply rendered transcriptionally silent by an antisense transcript whose own expression is dictated by the upstream imprinting centre — is the central biological rationale for the entire class of unsilencing therapeutics discussed in Section 7.

4.4 Chromatin Architecture and the Broader Epigenetic Landscape of the Imprinting Centre

Beyond DNA methylation itself, the bipartite imprinting centre and its surrounding chromatin show allele-specific differences in nuclease accessibility and transcription factor occupancy that further reinforce the parent-specific transcriptional output of the locus; regulatory elements within DNase I hypersensitive regions of the murine PWS-IC homologue, for instance, contribute to activation of upstream paternally expressed genes such as NDN and MKRN3 (Lewis et al., 2015). More recent functional genomic screens using CRISPR-based repression and activation libraries in human induced pluripotent stem cells have begun to map further, previously uncharacterised regulatory elements at the 15q11–q13 locus that govern SNRPN expression from each parental chromosome. These screens show that targeted transcriptional activation and targeted DNA demethylation act preferentially at distinct sub-regions and engage distinguishable epigenetic reprogramming mechanisms, suggesting that the regulatory landscape around the bipartite imprinting centre is considerably more elaborate than a single promoter-methylation switch, and that it offers more than one mechanistically distinct point of potential therapeutic entry (Rohm et al., 2025).

5. Molecular Genetics and Pathogenic Mechanisms of Angelman Syndrome

5.1 Overview of the four Principal Molecular Subtypes

Angelman syndrome arises through four recognised, mechanistically distinct routes, all of which converge on the functional loss of maternal UBE3A expression in neurons: a large interstitial deletion of the maternal 15q11–q13 region, which accounts for the majority of cases; intragenic mutation of the maternal UBE3A gene itself; paternal uniparental disomy of chromosome 15, in which an individual inherits two paternal copies of the chromosome and no maternal copy; and imprinting defects, in which both chromosomes are biparentally inherited but the maternal one carries an aberrant, paternal-pattern epigenotype at the imprinting centre (Duis et al., 2022). Each subtype carries distinct implications for recurrence risk, for the severity and detail of the associated phenotype, and increasingly for eligibility and likely response to mechanism-specific therapeutics, since interventions that act by unsilencing the paternal UBE3A allele are mechanistically applicable to deletion, uniparental disomy and imprinting-defect cases — where a structurally intact paternal allele is present — but not to patients whose disease results from an intragenic UBE3A mutation, where the relevant maternally derived coding sequence is itself at fault.

5.2 Maternal 15q11–q13 Deletion

The most common subtype, accounting for roughly seventy to seventy-five per cent of cases, is a large, typically several-megabase interstitial deletion of the maternal copy of 15q11–q13 that removes UBE3A, the imprinting centre, and the flanking non-imprinted genes within the commonly deleted interval (Duis et al., 2022). It is generally a *de novo* event and therefore carries a low recurrence risk for future pregnancies, but it is also associated with the most severe end of the clinical spectrum, including a higher prevalence of microcephaly, hypopigmentation (reflecting co-deletion of the nearby OCA2 gene), and seizures, relative to the other molecular subtypes (Bird, 2014).

5.3 UBE3A Mutation

Intragenic pathogenic variants in the maternal UBE3A allele — ranging from nonsense and frameshift mutations to missense substitutions affecting the catalytic HECT domain of the encoded ubiquitin ligase — account for roughly ten to fifteen per cent of cases. When maternally inherited, they carry a fifty per cent recurrence risk for subsequent pregnancies, consistent with straightforward autosomal dominant transmission

whose expressivity happens to be imprinted (Duis et al., 2022). This subtype stands apart from the other three in one important respect: the paternal UBE3A allele, although intact, offers no useful therapeutic target for unsilencing strategies, since here it is the maternal allele itself, not merely its expression, that is defective. Affected individuals in this subgroup would, in principle, need gene replacement, gene correction, or protein-level intervention rather than unsilencing of the paternal copy.

5.4 Paternal Uniparental Disomy

Paternal uniparental disomy, in which an individual inherits two structurally normal but both paternally derived copies of chromosome 15, accounts for a small minority of cases — generally cited at around five to seven per cent — and arises through errors of meiotic non-disjunction followed by loss of the maternal homologue (Duis et al., 2022). Because both copies of the imprinting centre carry the paternal epigenotype in this subtype, the locus produces no maternal UBE3A expression at all in neurons, even though both alleles are structurally entirely normal. This makes the subtype, alongside deletion and imprinting-defect cases, mechanistically amenable in principle to therapeutic unsilencing of either paternal allele.

5.5 Imprinting Defects and Microdeletions of the Imprinting Centre

Imprinting defects, accounting for a further five to seven per cent of cases, involve biparental inheritance of structurally normal chromosomes 15 in which the maternal allele has nonetheless acquired a paternal-pattern, unmethylated epigenotype at the SNRPN imprinting centre (Buiting et al., 1998; Buiting et al., 1999; Duis et al., 2022). Most of these reflect a sporadic failure of imprint establishment or maintenance with no detectable underlying sequence abnormality, and a correspondingly low recurrence risk. A clinically important minority, however, arise from an inherited microdeletion of the AS-IC itself — a lesion invisible to the methylation-based assays used as first-line tests, since those assays interrogate methylation status at the PWS-IC rather than the physical integrity of the AS-IC, and one that carries a substantially elevated, essentially Mendelian recurrence risk when transmitted through further maternal meioses (Buiting et al., 1998; Buiting et al., 1999). Distinguishing sporadic imprinting defects from inherited AS-IC microdeletions, despite their identical methylation signature on first-line testing, was central to the historical development of supplementary techniques capable of directly interrogating the AS-IC sequence, and remains a key consideration in genetic counselling for families found to have an imprinting defect today (Buiting et al., 1998; Duis et al., 2022).

Table 2. Molecular genetic mechanisms underlying Angelman syndrome

Molecular subtype	Approximate frequency	Methylation pattern at SNRPN	Recurrence risk	Therapeutic relevance of paternal UBE3A allele
Maternal 15q11–q13 deletion	70–75%	Abnormal (paternal-only)	Low (typically de novo)	Intact; amenable to unsilencing strategies
UBE3A intragenic mutation	~10–15%	Normal (biparental)	High if maternally inherited (~50%)	Intact but irrelevant; maternal allele itself defective
Paternal uniparental disomy	~5–7%	Abnormal (paternal-only)	Generally low	Intact; amenable to unsilencing strategies
Imprinting defect (epimutation or AS-IC deletion)	~5–7%	Abnormal (paternal-only)	Low if epimutation; high if inherited AS-IC deletion	Intact; amenable to unsilencing strategies

Sources: Buiting et al. (1998); Buiting et al. (1999); Bird (2014); Duis et al. (2022)

The distribution in Table 2 carries an important corollary for the therapeutic discussion later in this review: across the deletion, uniparental disomy and imprinting-defect subtypes combined, the great majority of patients with Angelman syndrome — by most estimates, somewhere in the region of eighty to ninety per cent — retain a structurally intact paternal UBE3A allele that is, in principle, accessible to unsilencing-based therapeutics. Only the UBE3A-mutation subgroup falls outside the reach of this entire therapeutic strategy.

6. Clinical Phenotype and Diagnosis

6.1 Clinical Features and Consensus Diagnostic Criteria for Angelman Syndrome

The clinical phenotype of Angelman syndrome was first codified into consensus diagnostic criteria in 1995 and updated in 2006. These criteria distinguish features present in almost all affected individuals — developmental delay evident from the first year of life, severe speech impairment with absent or minimal use of words, a movement or balance disorder typically presenting as gait ataxia, and a characteristic behavioural profile combining a happy demeanour, easily provoked laughter, hypermotor behaviour, and a short attention span — from frequent but non-universal features such as microcephaly, seizures with a characteristic electroencephalographic signature, and sleep disturbance (Williams et al., 1995, 2006). Developmental progress typically plateaus at a level corresponding to a developmental age of around two to two-and-a-half years, and cognitive function generally falls within the severe range of impairment, with expressive language disproportionately affected relative to receptive understanding (Bird, 2014). The disorder substantially affects family quality of life and caregiving burden, and unmet clinical needs — particularly around communication support, sleep and seizure management — remain considerable despite improvements in symptomatic care (Wheeler et al., 2017).

6.2 Prader–Willi Syndrome as the Reciprocal Disorder

Prader–Willi syndrome, arising from loss of paternal gene expression across the same genomic interval, follows a markedly different clinical trajectory: severe neonatal hypotonia and feeding difficulty give way, during early childhood, to hyperphagia and a strong predisposition to obesity, accompanied by short stature, hypogonadism, characteristic facial features, and generally milder intellectual disability than is seen in Angelman syndrome, alongside a distinctive behavioural and, in some cases, psychiatric phenotype (Bittel & Butler, 2005; Cassidy & Driscoll, 2009; Cassidy et al., 2012). Clinical diagnostic criteria for Prader–Willi syndrome have similarly evolved as molecular understanding of the locus has improved, shifting from a points-based system weighted towards major and minor clinical features in early childhood towards an approach in which molecular genetic confirmation, given its near-universal sensitivity, has become central to diagnosis rather than merely confirmatory of a clinical impression (Gunay-Aygun et al., 2001; Angulo et al., 2015). The juxtaposition of these two disorders, arising from disruption of opposite parental alleles within an identical genomic interval, remains the clearest human illustration available of how genomic imprinting can convert a single chromosomal region into the substrate for two entirely distinct disease phenotypes.

6.3 Laboratory Diagnostic Algorithm

Because the clinical features of Angelman syndrome, particularly in early infancy, can overlap with those of cerebral palsy or idiopathic autism spectrum disorder, laboratory confirmation is considered essential to diagnosis (Bird, 2014; Buiting et al., 2016). The first-line investigation is parent-specific DNA methylation analysis at the SNRPN locus, most often performed using methylation-specific multiplex ligation-dependent probe amplification, which simultaneously provides copy-number information capable of detecting the large deletions that account for the majority of cases. Because this assay tests the methylation status of the PWS-IC rather than relying on indirect inference, it detects the molecular signature shared by deletion, uniparental disomy and imprinting-defect subtypes in a single test, together accounting for roughly eighty per cent of cases (Duis et al., 2022; Williams et al., 2010). Where methylation analysis is normal but clinical suspicion remains high, sequence analysis of UBE3A is undertaken to identify intragenic mutations. Where an abnormal methylation pattern is found, fluorescence in situ hybridisation or microarray analysis, together with microsatellite or single-nucleotide-polymorphism-based parental origin studies, is used to distinguish a large deletion from uniparental disomy or a true imprinting defect — a distinction that matters considerably for recurrence-risk counselling (Duis et al., 2022). In the rare subset of patients with an imprinting defect in whom an inherited AS-IC microdeletion is suspected, typically because of a family history suggestive of recurrence, supplementary sequence-level analysis of the AS-IC region is required, since this lesion lies outside the region interrogated by standard methylation assays (Buiting et al., 1999; Beygo et al., 2020). A multidisciplinary consensus statement on standards of care has further formalised this diagnostic algorithm and placed it within a broader framework addressing the medical, developmental and behavioural management of affected individuals across the lifespan (Duis et al., 2022).

7. Epigenetic Therapeutic Strategies Targeting the SNRPN/UBE3A-ATS Axis

7.1 Therapeutic Rationale: Unmasking a Dormant, Intact Allele

The therapeutic logic behind most recent translational work in Angelman syndrome departs in a fundamental way from the gene-replacement paradigm applied to many other monogenic disorders. Because the paternal UBE3A allele is structurally intact in the majority of affected individuals, and is rendered transcriptionally silent in neurons specifically through the action of the UBE3A-ATS antisense transcript — whose own expression is governed by the SNRPN bipartite imprinting centre — the field has converged on strategies designed to reduce or eliminate UBE3A-ATS expression or activity. Doing so allows transcription of the paternal UBE3A allele to proceed, restoring functional ubiquitin ligase protein to neurons that would otherwise be entirely deficient in it (Meng et al., 2015; Markati et al., 2021). This unsilencing paradigm is attractive precisely because it requires no correction of the underlying genetic lesion on the maternal chromosome and no delivery of an exogenous transgene; it relies instead on reversing a naturally occurring, in principle reversible, epigenetic and transcriptional regulatory state.

7.2 Small-molecule Unsilencers

The feasibility of paternal UBE3A unsilencing was first demonstrated through an unbiased small-molecule screen in primary cortical neurons from a fluorescent UBE3A reporter mouse. The screen identified a series of topoisomerase I and topoisomerase II inhibitors, including the clinically approved anticancer agent topotecan, capable of activating the silenced paternal Ube3a allele in cultured neurons and, on systemic administration, throughout multiple brain regions in vivo, with effects persisting for several weeks after the drug was stopped (Huang et al., 2012). This discovery offered proof of principle that pharmacological unsilencing was achievable, but the inherent genotoxicity and limited target specificity of topoisomerase inhibitors — which act broadly across long genes throughout the genome rather than selectively at the UBE3A-ATS locus — ruled out their direct clinical development for a chronic paediatric neurodevelopmental indication (Wang & Jiang, 2023). That limitation prompted a search for small molecules working through alternative mechanisms, which led to the compound (S)-PHA533533. This molecule substantially increases paternal Ube3a messenger RNA and protein levels while simultaneously lowering Ube3a-ATS in neurons derived from Angelman syndrome model mice, is active following peripheral rather than intrathecal administration, and unsilences paternal UBE3A in neurons derived from human Angelman syndrome patients. Orally or systemically deliverable small-molecule unsilencers, with potentially more favourable safety and delivery profiles than nucleic-acid-based approaches, remain an active line of investigation as a result (Vihma et al., 2024).

7.3 Antisense Oligonucleotide Therapies

The most clinically advanced therapeutic class targets UBE3A-ATS directly, using antisense oligonucleotides that bind the antisense transcript and promote its degradation through an RNase H-dependent mechanism, relieving the transcriptional interference that silences the paternal UBE3A allele (Meng et al., 2015). Foundational preclinical work showed that intracerebroventricular or intrathecal administration of such oligonucleotides in mouse models produces sustained reduction of Ube3a-ATS, robust reinstatement of UBE3A protein throughout the brain, and at least partial correction of associated behavioural and electrophysiological phenotypes, with notably greater efficacy and durability when treatment begins in the early postnatal period rather than in adulthood (Meng et al., 2015; Milazzo et al., 2021). Subsequent work extended these findings by demonstrating rescue of disturbed cortical brain rhythms and sleep architecture following antisense oligonucleotide treatment in both juvenile and, to a more limited extent, adult mouse models — encouraging, in that it suggests some therapeutic benefit may be achievable beyond the earliest developmental window, even if the magnitude of that benefit remains age-dependent (Lee et al., 2023). A separate antisense oligonucleotide programme targeting an evolutionarily conserved region near the start of the UBE3A-AS transcript achieved robust and efficient repression of the antisense transcript and reactivation of paternal UBE3A throughout the central nervous system of non-human primates, providing a translational bridge between rodent proof-of-concept work and subsequent human dosing; this molecule subsequently advanced into a registered paediatric clinical programme (Dindot et al., 2023). A parallel discovery effort screened a library of locked-nucleic-acid-modified antisense oligonucleotides directly in patient-derived neurons, in order to overcome the poor cross-species sequence conservation of UBE3A-ATS, and identified the molecule subsequently named rugonersen.

Rugonersen selectively and potently reduced UBE3A-ATS and raised UBE3A messenger RNA and protein levels in neurons derived from neurotypical individuals, individuals with Angelman syndrome, and cynomolgus monkeys, with effects in non-human primates that proved long-lasting following intrathecal dosing (Jagasia et al., 2025).

7.4 Genome and Epigenome Editing Approaches

A further therapeutic class employs CRISPR-associated nucleases, or catalytically inactivated Cas9 variants, to disrupt UBE3A-ATS expression at the level of DNA rather than RNA. An early demonstration used a short Cas9 variant and guide RNA targeting the SNORD115 small nucleolar RNA cluster embedded within Ube3a-ATS, packaged into an adeno-associated viral vector and delivered to Angelman syndrome model mice during the embryonic or early postnatal period. Genomic integration of the vector at the target site caused premature termination of Ube3a-ATS transcription, either through collision with a vector-encoded polyadenylation signal or, when integrated in the reverse orientation, through transcriptional collision with the vector-encoded Cas9 transcript itself. This single intervention unsilenced paternal Ube3a throughout the brain for at least seventeen months — the longest duration of effect reported for any Angelman syndrome therapeutic at the time — and rescued multiple anatomical and behavioural phenotypes (Wolter et al., 2020). A related approach using catalytically active Cas9 directed at the same antisense transcript region produced insertion-deletion mutations sufficient to unsilence paternal Ube3a-YFP reporter expression and partially correct behavioural phenotypes after neonatal, though not later, viral delivery, reinforcing a theme that recurs across nearly every therapeutic modality discussed here: a restricted developmental window for maximal benefit (Schmid et al., 2021).

Conceptually distinct from these gene-disrupting approaches is true epigenome editing, in which a catalytically dead Cas9 is fused not to a nuclease domain but to an epigenetic effector domain, allowing site-specific deposition of a regulatory chromatin mark without altering the underlying DNA sequence at all. Using a dCas9 fusion construct that recruits the catalytic domains of two DNA methyltransferases, targeted methylation of the murine Snrpn imprinting centre was shown to inhibit Ube3a-ATS expression, unsilence paternal Ube3a, and alleviate behavioural phenotypes in transgenic Angelman syndrome mice — demonstrating that the imprinting centre can, in a real sense, be re-imprinted through direct epigenetic intervention rather than indirect modulation of its downstream antisense transcript (Liu et al., 2024). This strategy has obvious conceptual appeal: it intervenes at the regulatory switch identified earlier in this review as the master controller of the entire 15q11–q13 domain, and, unlike nuclease-based gene editing, avoids introducing any permanent change to DNA sequence — a feature of some relevance to long-term safety in a paediatric population that would presumably require lifelong, single-administration therapy. The same logic of CRISPR-based epigenome editing has also been applied in the opposite direction to Prader–Willi syndrome, where systematic repression and activation screens at the SNRPN locus in human induced pluripotent stem cells have identified genomic elements whose targeted transcriptional activation or targeted DNA demethylation can reactivate the silenced maternal SNRPN allele and downstream paternally expressed transcripts. The demethylation-based approach in particular produces stable, long-term maternal SNRPN expression after only transient expression of the editing machinery (Rohm et al., 2025). Related strategies using dCas9 fusions to disrupt Ube3a-ATS through a non-template-biased transcriptional interference mechanism — without requiring a chromatin-modifying domain at all — have further diversified the mechanistic toolkit available for paternal Ube3a unsilencing (Wang & Jiang, 2023).

7.5 Gene Replacement and Other Emerging Modalities

Although the unsilencing paradigm has dominated recent translational effort, gene replacement and enzyme replacement strategies — intended to deliver a functional UBE3A transgene or protein directly, rather than reactivate the endogenous paternal allele — remain under preclinical and early clinical investigation as part of a broader and mechanistically diverse pipeline that has been estimated to comprise at least fifteen distinct approaches at various stages of development (Markati et al., 2021). These approaches are not mutually exclusive with unsilencing strategies, and may, in principle, offer an alternative route to benefit for the minority of patients whose disease stems from intragenic UBE3A mutation, for whom paternal allele unsilencing offers nothing, since their paternal allele, while transcriptionally accessible, is not the source of the deficient maternal protein.

The breadth of approaches in Table 3 illustrates a field that has moved, within little more than a decade, from a single proof-of-concept pharmacological observation to a multi-modal pipeline spanning small molecules, three

distinct nucleic-acid and gene-editing classes, and renewed interest in direct protein or gene replacement, with antisense oligonucleotides currently the most clinically mature.

Table 3. Major classes of therapeutic strategy targeting the SNRPN–UBE3A-ATS axis in Angelman syndrome

Therapeutic class	Representative agent/approach	Molecular mechanism	Developmental stage (as of 2026)
Small-molecule topoisomerase inhibitors	Topotecan and related agents	Genome-wide unsilencing of long genes including Ube3a	Discontinued for AS owing to genotoxicity
Small-molecule unsilencer (novel mechanism)	(S)-PHA533533	Increases paternal Ube3a mRNA/protein; downregulates Ube3a-ATS	Preclinical
Antisense oligonucleotides	Apazunersen (GTX-102), ION582, rugonersen	RNase H-mediated degradation of UBE3A-ATS	Phase 1/2–3 clinical trials
Nuclease-based gene editing	AAV-delivered Cas9/sgRNA targeting SNORD115/Ube3a-ATS	Disruption/termination of Ube3a-ATS transcription via indels or vector integration	Preclinical (mouse)
Epigenome editing	dCas9–DNA methyltransferase fusion targeting Snrpn-IC	Direct re-methylation of imprinting centre, silencing Ube3a-ATS	Preclinical (mouse)
Gene/enzyme replacement	Various AAV- or protein-based candidates	Direct delivery of functional UBE3A transgene or protein	Preclinical/early clinical

Sources: Huang et al. (2012); Meng et al. (2015); Markati et al. (2021); Milazzo et al. (2021); Wolter et al. (2020); Schmid et al. (2021); Dindot et al. (2023); Vihma et al. (2024); Liu et al. (2024); Wang & Jiang (2023); Jagasia et al. (2025)

8. Clinical Translation: Trials, Biomarkers and Persistent Challenges

8.1 The Current Clinical Trial Landscape

As of recent findings, three antisense oligonucleotide programmes targeting UBE3A-ATS have reached registered late-stage or controlled clinical evaluation in Angelman syndrome. Apazunersen (GTX-102), delivered intrathecally, completed an open-label phase 1/2 dose-escalation study and is now being evaluated in the randomised, double-blind, sham-controlled phase 3 ASPIRE study in paediatric participants with Angelman syndrome (ClinicalTrials.gov, 2026a; Dindot et al., 2023). Sponsor and registry sources describe GTX-102 as a phase 3 programme with FDA breakthrough therapy, orphan drug, rare paediatric disease and fast-track designations; these regulatory designations should be interpreted as development-facilitating statuses rather than as evidence of approved efficacy (ClinicalTrials.gov, 2026a). ION582, also delivered intrathecally and designed to inhibit UBE3A-ATS, is being evaluated in the global phase 3 REVEAL study after phase 1/2 HALOS development; sponsor-reported HALOS results supported FDA breakthrough therapy designation, but peer-reviewed pivotal efficacy data remain unavailable (ClinicalTrials.gov, 2026b). Rugonersen completed a phase 1, open-label, multiple-ascending-dose study in sixty-one children with Angelman syndrome; the primary safety and tolerability endpoint was met, and exploratory analyses showed partial normalisation of the characteristic electroencephalographic delta-power abnormality together with clinical signals that require confirmation in larger controlled trials (Hipp et al., 2025). A randomised, double-blind, sham-controlled phase III BEACON study of rugonersen is registered to evaluate efficacy and safety in paediatric and adult participants (ClinicalTrials.gov, 2026c). Overall, the clinical landscape is encouraging but remains provisional: no disease-modifying therapy is approved, and the magnitude, durability and developmental timing of clinical benefit must be established in ongoing pivotal studies.

8.2 Electroencephalographic Delta Power as a Pharmacodynamic Biomarker

A recurring and methodologically important theme across these programmes has been the use of quantitative electroencephalographic delta-band (2–4 Hz) power as a non-invasive, objective biomarker of target engagement and treatment effect. This builds on prior natural history work showing that delta power correlates

robustly with cognitive function in individuals with Angelman syndrome (Ostrowski et al., 2021). Because delta power varies considerably both across individuals and across developmental stage, a longitudinal natural history model incorporating age, elapsed time and baseline relative delta power was developed from a dataset of 204 electroencephalographic recordings obtained from fifty-six individuals with Angelman syndrome, allowing deviations from the expected natural trajectory to be attributed, with reasonable statistical confidence, to treatment effect rather than to background developmental variability. The same modelling framework, applied to a parallel mouse dataset, successfully detected an antisense-oligonucleotide-mediated treatment effect on both delta activity and Ube3a expression, and deviations in delta power correlated significantly with the degree of Ube3a re-expression achieved (Spencer et al., 2022). The subsequent observation, in the rugonersen phase 1 trial, of a dose-dependent partial normalisation of this same electroencephalographic signature in human participants is one of the first instances in a neurodevelopmental disorder of a treatment targeting the underlying genetic and epigenetic cause producing a measurable, biologically interpretable change in objective brain activity — and it lends some independent corroboration to the mechanistic hypothesis underlying the whole unsilencing strategy (Hipp et al., 2025).

8.3 Developmental Windows and the Question of Therapeutic Timing

A consistent and clinically important theme running through the preclinical literature is that the degree of phenotypic rescue achieved by paternal UBE3A unsilencing depends strongly on the developmental stage at which intervention occurs. Several rodent studies show markedly greater and more comprehensive correction of behavioural, electrophysiological and synaptic plasticity phenotypes when treatment begins during the embryonic or early postnatal period rather than in juvenile or adult animals (Wolter et al., 2020; Milazzo et al., 2021; Lee et al., 2023). This fits the broader concept of critical or sensitive periods in neurodevelopment, during which certain circuit-level consequences of UBE3A deficiency may become progressively harder to reverse with age, even though the molecular lesion itself — transcriptional silencing of an otherwise intact gene — remains, in principle, fully correctable at any age. The clinical implication, still not fully resolved, is that the patient populations and trial designs most likely to show substantial benefit from currently available therapeutics may be younger than those in which initial safety and feasibility studies, for understandable ethical and practical reasons, have generally been conducted. Current and forthcoming trials enrolling progressively younger cohorts are beginning to address that tension directly.

8.4 Safety, Delivery and Target Specificity Considerations

The translational pathway for nucleic-acid-based therapeutics in this indication has not been without setbacks. The GTX-102 programme, for example, experienced a temporary clinical hold after lower-extremity weakness was observed in a subset of participants, before resuming once protocol modifications narrowed the dose range and adjusted the route of administration. More broadly, every modality reviewed in Section 7 carries its own characteristic safety profile and delivery constraint. Small-molecule topoisomerase inhibitors carry inherent genotoxicity that has effectively ruled out their clinical translation despite a clear proof of mechanism; antisense oligonucleotides require repeated, invasive intrathecal administration and carry a class-characteristic, though generally manageable, risk profile shared with other approved central nervous system antisense therapeutics; nuclease-based gene editing introduces permanent, irreversible genomic modification with attendant theoretical off-target risk; and epigenome editing, while avoiding permanent sequence alteration, remains at an early preclinical stage, with the durability, delivery and long-term stability of the induced epigenetic mark not yet established in any large animal or human system (Wang & Jiang, 2023; Markati et al., 2021).

9. Towards a Unified Epigenetic Framework for 15q11–q13 Imprinting Disorders

9.1 The Imprinting Centre as a Shared Therapeutic Target Across Reciprocal Disorders

A conceptually important development in this field has been the recognition that the bipartite imprinting centre, rather than mattering only for the downstream consequences of its dysfunction, can itself be approached as a direct therapeutic target — and that strategies developed for this purpose are, with appropriate modification, applicable in principle to both Angelman syndrome and its reciprocal disorder, Prader–Willi syndrome, despite the opposite direction of allelic silencing that characterises each condition. In Angelman syndrome, the goal is to silence, or prevent transcriptional output from, the paternal imprinting centre element responsible for driving

UBE3A-ATS expression. In Prader–Willi syndrome, the goal runs the other way: to activate the silenced maternal SNRPN locus and its downstream paternally expressed gene cluster (Rohm et al., 2025; Liu et al., 2024). That both objectives have now been demonstrated, at least in cellular or murine model systems, using closely related CRISPR-based epigenome editing platforms that differ chiefly in the directionality of the recruited effector domain, lends real conceptual coherence to the idea that 15q11–q13 imprinting disorders, for all their starkly different clinical presentations, may ultimately be addressed through a shared family of locus-directed epigenetic editing tools (Wang & Jiang, 2023; Chao et al., 2022).

9.2 Epigenome Editing in Context: Promise and Unresolved Questions

The appeal of directing therapeutic intervention at the imprinting centre itself, rather than at its more distal downstream consequences, lies in the possibility of a more complete and physiologically faithful correction. Reinstating an appropriate epigenotype at the master regulatory switch could, in principle, restore the entire downstream programme of gene expression rather than addressing a single gene in isolation. This matters particularly for Prader–Willi syndrome, where multiple paternally expressed genes across the locus contribute to the overall phenotype, but it is also relevant to Angelman syndrome, where re-silencing the paternal imprinting centre element responsible for UBE3A-ATS production achieves the desired outcome by restoring, rather than circumventing, the natural regulatory logic of the locus (Liu et al., 2024). Considerable uncertainty nonetheless remains around the long-term stability of artificially induced epigenetic marks in post-mitotic neurons in vivo, the feasibility of achieving adequate and safe central nervous system delivery of large editing constructs in humans, the degree of off-target epigenetic modification that might occur at other imprinted or non-imprinted loci sharing sequence or chromatin features with the intended target, and the comparative cost, complexity and regulatory pathway of epigenome editing relative to the more clinically mature antisense oligonucleotide platforms already in late-stage human trials (Wang & Jiang, 2023; Chao et al., 2022).

Table 4 sets out this mirror-image logic side by side. Read across the two rows, what stands out is not the difference in direction but the similarity in toolkit: despite acting on opposite alleles and aiming for opposite outcomes, both strategies converge on the same physical target and draw on closely related dCas9-based editing platforms, which is precisely why advances made in one disorder tend to translate, with relatively modest adaptation, into the other.

Table 4. Comparative summary of unsilencing/reactivation strategies for Angelman syndrome and Prader–Willi syndrome at the SNRPN locus

Disorder	Allele requiring intervention	Direction of desired epigenetic change	Representative approach
Angelman syndrome	Paternal imprinting centre/UBE3A-ATS	Silence (reduce transcriptional output)	dCas9–DNA methyltransferase targeting Snrpn-IC; ASO degradation of UBE3A-ATS
Prader–Willi syndrome	Maternal imprinting centre/SNRPN	Activate (reactivate silenced locus)	CRISPR activation screens; targeted DNA demethylation of SNRPN regulatory elements

Sources: Rohm et al. (2025); Liu et al. (2024); Wang & Jiang (2023); Chao et al. (2022)

9.3 An Integrated Therapeutic Outlook

Taken together, the work reviewed here supports a cautiously optimistic, though far from settled, outlook. Three decades of structural and mechanistic dissection of the SNRPN bipartite imprinting centre have produced an unusually detailed picture of how a single, spatially distributed regulatory switch governs the parent-of-origin-specific expression of an entire imprinted domain. That mechanistic clarity has translated, with notable directness, into a therapeutic pipeline in which several independent modalities — pharmacological, oligonucleotide-based, and genome- or epigenome-editing-based — now converge on the same basic strategy: reversing a defined, and in principle fully reversible, epigenetic lesion. The advancement of three independent antisense oligonucleotide candidates into controlled, late-stage human trials, accompanied by the first objective electroencephalographic evidence of target engagement in human participants, represents tangible progress towards what would be the first disease-modifying treatment for this disorder, even as the more conceptually

ambitious strategy of directly re-editing the imprinting centre itself remains, for now, confined to preclinical models.

10. Conclusions

The SNRPN bipartite imprinting centre occupies a singular place in human medical genetics: a regulatory element whose disruption produces two clinically opposite, yet mechanistically closely related, neurodevelopmental disorders. Its detailed molecular dissection over the past three decades has moved from the descriptive identification of two non-contiguous deletion-overlap regions to a sophisticated, mechanistically grounded model of germline imprint establishment, somatic maintenance, and tissue-specific antisense-mediated gene silencing. That understanding has, in turn, generated an unusually direct and biologically rational translational pathway for Angelman syndrome, built on the recognition that the disease-causing lesion in most patients is not the absence of a functional gene but the epigenetically imposed silence of one that remains structurally intact. The resulting therapeutic pipeline — spanning small-molecule unsilencers, three antisense oligonucleotide candidates now in controlled human trials, and a growing array of nuclease- and epigenome-editing platforms capable of acting at the imprinting centre itself — is one of the more compelling contemporary examples of detailed mechanistic insight into an epigenetic regulatory element being turned into plausible, mechanism-matched therapeutic strategies. The emergence of objective, mechanistically interpretable biomarkers, particularly electroencephalographic delta power, and the recent demonstration of dose-dependent biological effect in human participants receiving antisense oligonucleotide therapy, represent genuine and measurable progress. At the same time, no disease-modifying therapy for Angelman syndrome has yet been approved, the magnitude and durability of clinical benefit observed so far remains modest relative to the severity of the underlying disorder, and the consistent preclinical finding that earlier intervention works better raises difficult, still unresolved questions about how, in practice, treatment could be delivered early enough to achieve its full potential benefit. The path towards a true cure for Angelman syndrome — in the sense of substantially restoring normal neurodevelopmental trajectory rather than ameliorating established deficits — remains open but unproven, and will depend on the outcome of the pivotal trials currently under way, and on continued refinement of the epigenome-editing strategies that, conceptually at least, offer the most direct route to correcting the lesion at its true molecular origin within the imprinting centre.

11. Limitations

This review is subject to several limitations inherent to its narrative format and to the current state of the underlying evidence base. As a narrative rather than systematic review, the selection and weighting of included studies, while guided by an explicit and reproducible search and screening strategy, necessarily retains an element of author judgement about the relative significance of individual findings, and no formal risk-of-bias or quality appraisal of each included study was undertaken, of the kind expected in a systematic review. The clinical trial literature discussed in Sections 7 and 8 is moving quickly, and several of the programmes described remain at relatively early stages of controlled human evaluation, so conclusions about their eventual efficacy, safety and regulatory trajectory should be treated as provisional and open to revision as data from ongoing pivotal phase 3 studies emerge. Much of the mechanistic evidence underpinning the therapeutic rationale set out in this review comes from murine models, and meaningful interspecies differences in the sequence architecture of the imprinting centre, in the developmental timing of relevant neurobiological processes, and in how readily behavioural outcome measures translate between species mean that preclinical findings, however internally consistent, cannot be assumed to predict human therapeutic response with confidence. Finally, this review has necessarily concentrated on the molecular biology of the bipartite imprinting centre and on therapeutic strategies arising directly from that biology, and has therefore addressed in comparatively limited depth other important dimensions of Angelman syndrome care, including symptomatic management of epilepsy and sleep disturbance, behavioural and communication intervention, and the substantial psychosocial and economic burden borne by affected families — each an important area of ongoing clinical and health-services research in its own right.

Consent

It is not applicable.

Ethical Approval

It is not applicable.

Declaration of AI Use

This manuscript was prepared through the combined contributions of all author(s), including contributions to the study design, data, content development, results, interpretation, and related scholarly work. The author(s) acknowledge the use of Grammarly and ChatGPT to assist with grammar checking, language refinement, reference formatting. These AI-assisted tools were not used as authors and did not replace the intellectual contributions or scholarly judgment of the author(s). All AI-assisted outputs, including content, references, and interpretations, were carefully reviewed, revised, verified, and approved by the author(s). The author(s) accept full responsibility for the accuracy, integrity, and final content of the manuscript.

Competing Interests

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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