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Waking the Silent Gene in Angelman Syndrome

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Minireview Article

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Abstract

Angelman syndrome is a severe neurogenetic disorder characterised by developmental delay, motor impairment, absent or markedly limited speech, epilepsy and a characteristic happy demeanour with frequent laughter. It results from loss of function of the maternally inherited *UBE3A* gene located in the 15q11-q13 chromosomal region, while the paternal allele is normally epigenetically silenced in neurons by the long non-coding antisense transcript *UBE3A-ATS*. The estimated prevalence is approximately 1 in 15,000 to 1 in 20,000 individuals. Maternal chromosome 15 deletion accounts for approximately 70-75% of cases, whereas paternal uniparental disomy, imprinting defects and *UBE3A* sequence variants represent additional mechanisms. Diagnosis is generally established between 1 and 4 years of age through DNA methylation analysis and complementary molecular testing, when developmental delay, impaired balance and other clinical features become apparent. Current treatment remains supportive and multidisciplinary, including physiotherapy, occupational therapy, speech and augmentative communication support, seizure management, sleep regulation

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and assistive devices. This minireview summarises the genetic background of Angelman syndrome, present symptomatic therapy and emerging approaches designed to restore neuronal *UBE3A* activity. Particular attention is given to antisense oligonucleotides, including ION582, GTX-102 and rugonersen, as well as AAV-mediated gene replacement and CRISPR-Cas9-based gene-reactivation strategies. These approaches seek either to unsilence the paternal *UBE3A* allele or to deliver functional *UBE3A* to the nervous system. Although early clinical and preclinical findings are encouraging, none of the investigational strategies discussed here can yet be considered curative. Long-term evidence regarding efficacy, dosing, delivery, tolerability and safety remains essential before routine use in children with Angelman syndrome can be justified.

Keywords: Angelman syndrome; UBE3A; genomic imprinting; antisense oligonucleotides; gene therapy; paternal allele reactivation; UBE3A-ATS; AAV vector; CRISPR-Cas9; pediatric neurogenetics.

1. Introduction

Angelman syndrome results from a rare genetic alteration on chromosome 15, a microdeletion on the maternal chromosome or paternal uniparental disomy involving 15q11-q13. To date, approximately 280 different types of mutations have been identified, with the E2-binding domain at position Cys820 frequently involved. It is often associated with developmental delay, cognitive impairment, excessive cheerfulness and markedly reduced speech development. The British paediatrician Harry Angelman first described the syndrome, later named after him, from a scientific perspective in 1965 (Angelman, 1965). He called it happy puppet syndrome because of the distinctive movement patterns and frequent laughter of the children he treated at that time. Life expectancy is not reduced in people with Angelman syndrome. Both boys and girls can be affected. The syndrome occurs with an average frequency of 1 in 15,000 to 1 in 20,000, which translates to 4,000 to 5,500 cases in Germany alone.

Over time, a variety of characteristics common in people with Angelman syndrome has been documented (Margolis et al., 2015). Not all affected individuals exhibit all of these characteristics, and existing characteristics do not manifest to the same degree in all individuals. Frequent, often objectively unfounded smiling and laughter, including unmotivated laughter or episodes of laughter during excitement and stress, may occur. Cognitive impairment, hyperactivity, difficulty concentrating and a short attention span are common. Many affected individuals have good memory for faces and directions and good spatial orientation. In early childhood, there may be no attempts at speech and no babbling; later, spoken articulation in expressive language is usually very limited, although some ability to learn alternative forms of communication may be present. An above-average duration of the oral phase, with exploration of the environment through the mouth, has also been described (Maranga et al., 2020).

Children with Angelman syndrome have movement and balance disorders, ataxia and usually a stiff, clumsy, swaying, wide-based gait with jerky or choppy movements (Manssen et al., 2025). One in ten children does not learn to walk, and motor development is also delayed. Sensory disturbances in the body area, balance problems, a large triangular mouth with a protruding upper jaw and comparatively small teeth, which are often widely spaced, may be observed. Excessive mouth and chewing movements may occur because of insufficient control of the oral muscles and excessive salivation. Sleep disorders may be associated with a deficiency of at least one hormone involved in healthy sleep regulation. A comparatively small head with posterior microcephaly may also be present (Pearson et al., 2019). A flattened tongue with unusual tongue protrusion is found in about 50% of affected individuals.

Epilepsy usually begins between the third and thirty-sixth month after birth, often improves again in adolescence around the age of 16 years and occurs in up to 90% of affected individuals. Electroencephalographic abnormalities can be detected independently of epilepsy and during sleep. Growth disorders may also occur. Children with Angelman syndrome are often notable for an intense search for physical contact. They usually have a strong sense of humour, are often very sociable and friendly, and laugh frequently, although often without apparent reason and particularly when excited (Sell & Heymans, 2024; Bridges et al., 2025). Hyperactivity is a striking characteristic of the syndrome, and sometimes extreme sleep disturbance is common, particularly in childhood (Williams et al., 2001).

These sleep disturbances are caused by a hormone deficiency and cannot be regulated through educational measures alone. Many children with Angelman syndrome need to be restrained at night, for example with shoulder and abdominal restraint, to help them settle. Despite their inability to learn regular speech, people with Angelman syndrome can usually learn simple, sometimes highly subjective signs based, for example, on the principles of sign-supported communication. They may also use pictures or gestures for communication. People with Angelman syndrome remain dependent on the help of others throughout life. They are intellectually educable to varying, but usually very limited, degrees and often require special support and ongoing personal assistance.

Angelman syndrome is an important rare disease because of its epigenetic origin as an imprinting disorder. Moreover, it has a close epigenetic association with Prader-Willi syndrome. Both diseases originate in the same chromosomal region on the long arm of chromosome 15, and the imprinting centres of both diseases are part of the bipartite SNRPN imprinting centre, a critical regulatory region located on human chromosome 15 (15q11-q13) that governs the genomic imprinting of different genes.

Despite expanding clinical and molecular knowledge, a practical gap remains between supportive management and the safe, durable application of disease-modifying approaches that can restore neuronal *UBE3A* function. Current evidence is still developing, particularly with regard to treatment timing, delivery to the brain, dose control, long-term safety and the extent to which different genetic subtypes may respond. This minireview therefore aims to summarise present therapeutic options for Angelman syndrome and future strategies intended to wake the silent paternal gene for potential therapeutic intervention in childhood.

2. Genetic Background in Angelman Syndrome

Angelman syndrome is caused by the absence or malfunction of the *UBE3A* gene on the maternal chromosome 15 in region 15q11-q13 (Buiting et al., 2016; Fitzgerald, 2024; Ohta et al., 1999). In almost all affected individuals, loss of the active *UBE3A* gene in the brain is the trigger (Jiang et al., 1999). *UBE3A* encodes an E3 ubiquitin ligase (Almeida et al., 2025). Most often, loss-of-function point mutations in the HECT domain of *UBE3A* are sufficient to produce Angelman syndrome. Angelman syndrome is characterised by maternal mutations or deletions of the *UBE3A* gene. The paternal *UBE3A* allele is epigenetically silenced in cis by a long non-coding antisense RNA, *UBE3A-ATS* (Wang et al., 2021).

This can result from four different genetic mechanisms. Maternal deletion is found in approximately 70-75% of patients, in whom a large segment of the maternal chromosome 15 containing the *UBE3A* gene is lost. Paternal uniparental disomy is present in 3-7% of patients. The child receives both copies of chromosome 15 from the father instead of one from each parent. Because the paternal gene is imprinted in certain brain regions, a deficiency occurs. Another possibility is an imprinting centre defect, present in approximately 1-3% of patients. The region on maternal chromosome 15 is present but is erroneously silenced, like the paternal version. A *UBE3A* gene mutation is found in approximately 5-11% of patients with Angelman syndrome. The gene is physically present but defective and non-functional because of a mutation in the genetic code. In most body cells, both copies of the *UBE3A* gene, maternal and paternal, are active. However, in specific areas of the brain, such as the cerebellum and hippocampus, the paternal gene is naturally silenced. If the maternal gene also fails to function because of a defect or loss, no functional UBE3A protein is produced in the brain, causing the neurological symptoms (Krzeski et al., 2024; Madaan & Morales, 2026).

2.1 Present Therapy Options

There is currently no cure for Angelman syndrome, but symptoms can be significantly alleviated through multidisciplinary therapy. The focus is on physical and occupational therapy, speech therapy often involving augmentative and alternative communication aids, medication for epilepsy and sleep disorders, and promotion of sensory integration. Key areas of treatment include physical therapy and psychomotor therapy. Because Angelman syndrome often leads to developmental delay and unsteady gait, targeted movement exercises help improve mobility, build muscle tone and prevent postural abnormalities, such as scoliosis. Speech therapy and augmentative and alternative communication may be necessary because spoken language is severely impaired or absent; visual communication tools, picture boards or specialised communication aids are therefore used. A large proportion of affected individuals experience seizures. These are typically managed with antiepileptic drugs, such as levetiracetam or lamotrigine. In severe cases, a ketogenic diet may also be considered. Sleep disorders are common. Melatonin supplementation or sleep hygiene measures can help regulate disrupted sleep-

wake cycles. Occupational therapy and assistive devices, including gait trainers, specialised therapeutic bicycles and standing frames, can facilitate daily activities and promote independence.

3. Gene Therapy Approaches in Angelman Syndrome

Scientists are working intensively on causative gene-therapy approaches (Markati et al., 2021; Tsagkaris et al., 2020; Judson et al., 2026). These approaches aim to activate the otherwise inactive paternal gene in the brain to compensate for the genetic defect. Relevant clinical trials are currently underway (Keary & McDougle, 2023). Prenatal efforts have been conducted with the application of antisense oligonucleotides during pregnancy in mice (Clarke et al., 2024; Sonzogni et al., 2020). Gene therapies for Angelman syndrome are currently in development and clinical testing. They target the underlying cause: loss of function of the *UBE3A* gene (Meng et al., 2015; Yang & Huang, 2025). Although there is currently no approved therapy, rapid research is focusing on two main approaches: gene activation by antisense oligonucleotides, in which antisense oligonucleotides aim to reverse silencing of the paternal *UBE3A* gene, normally inactive in the brain, so that it can take over the gene's function; and gene replacement therapy, which involves introducing a healthy copy of the *UBE3A* gene directly into cells using viral vectors (Dindot et al., 2023; Nenninger et al., 2022; Elgersma & Sonzogni, 2021; Milazzo et al., 2021).

Regarding the current state of research and trials, progress is moving quickly (Lee et al., 2023). In addition to antisense oligonucleotides already in clinical trials, newer developments, such as gene replacement therapies, are entering clinical testing (Camões Dos Santos et al., 2025). Cutting-edge approaches, including CRISPR-Cas9 gene editing, are also being intensively researched at the preclinical stage to specifically activate the existing dormant gene (Reiter, 2023).

4. Antisense Oligonucleotides (ASO)

4.1 ION582 (Obudanersen)

ION582, also known by the international non-proprietary name obudanersen, is an investigational drug currently being developed by Ionis Pharmaceuticals. It is an antisense oligonucleotide designed for the potential disease-modifying treatment of Angelman syndrome. Ionis Pharmaceuticals explains the mechanism of action as unsilencing the gene. In the human brain, the paternal copy of the *UBE3A* gene is normally silenced by an RNA sequence called *UBE3A-ATS* (Smeenk et al., 2026). ION582 selectively targets this antisense strand for cleavage and degradation and removes the blockage. This reactivates, or unsilences, the paternal gene, enabling the body to resume production of *UBE3A* proteins in the brain. Current development status and clinical trials include the HALOS Phase 1/2 study. ION582 showed promising results. Almost all patients, 97% in the medium- and high-dose groups, demonstrated clinically meaningful improvements in areas such as communication, cognition and motor function. A global pivotal Phase 3 trial, REVEAL, is currently underway to evaluate the efficacy and safety of the drug in children and adults with Angelman syndrome. It includes study sites in Germany as well as Italy, Spain and Poland. The U.S. Food and Drug Administration has granted ION582 breakthrough therapy designation. In conclusion, no definitive information about effectiveness, tolerability or safety can be provided to date, and further long-term evaluations and studies will be needed after approval of the drug.

4.2 GTX-102 (Apazunersen)

GTX-102 is an investigational drug being developed to treat Angelman syndrome, a rare genetic neurodevelopmental disorder. Its mechanism of action is not conventional gene therapy. GTX-102 is an antisense oligonucleotide. It aims to activate the normally silent paternally inherited gene, thereby triggering production of the protein missing in the brains of individuals with Angelman syndrome. The drug is currently undergoing clinical testing, including advanced Phase 3 trials. As of 2026, it is not yet an approved medication. It is injected directly into the spinal canal. It is not yet approved to date, and long-term follow-up will be necessary after approval to examine efficacy, side effects and overall safety closely.

4.3 Rugonersen (RO7248824)

Rugonersen is an investigational antisense oligonucleotide. It aims to reactivate the silenced paternal *UBE3A* gene in the brain, thereby directly addressing the root cause of this rare neurodevelopmental disorder at the

genetic level (Hipp et al., 2025). Key developments and current studies include Phase 1 results. The TANGELO study, a Phase 1 trial involving children aged 1 to 12 years, demonstrated good tolerability and early signs of clinical improvement. Assessments included brain activity as well as motor and cognitive development. Acquisition was performed by Oak Hill Bio after Roche initially paused development of the drug. Oak Hill Bio secured global rights in 2025 to advance its clinical development. Under compassionate use and an expanded access programme, continued treatment was approved for patients who had previously participated in earlier studies. Rugonersen has not yet received official approval as a medication from health authorities. It remains an investigational drug undergoing clinical testing in a Phase 1 study at the time of publication, and further dose-finding studies are needed as the next step.

5. AAV Gene Therapy

5.1 MVX-220

MVX-220 is an experimental AAV gene therapy for the treatment of Angelman syndrome (Samanta, 2026; Beaudet & Meng, 2016; Bailus & Segal, 2014; Wolter et al., 2025). It is being developed by the biotechnology company MavriX Bio in collaboration with GEMMABio, based on technologies from Dr James Wilson at the University of Pennsylvania. The therapy aims to treat the underlying genetic cause of the disease by introducing a functional gene copy directly into the brain. Gene replacement delivers a healthy, fully functional copy of the human *UBE3A* gene directly to neurons in the brain. It uses a modified, harmless adeno-associated virus, AAVhu68, as a delivery vehicle. Administration is delivered as a single injection into the cisterna magna, thereby bypassing the blood-brain barrier via the cerebrospinal fluid space. The drug is currently being tested for safety, tolerability and preliminary efficacy in a combined multicentre, open-label Phase 1/2 trial named ASCEND-AS (NCT07181837). The first human participant was dosed in November 2025 as part of this open-label trial. The duration of the study is 5 years. The U.S. Food and Drug Administration has granted MVX-220 both Fast Track and Orphan Drug designations to accelerate clinical development and regulatory review. Overall, first results are planned for 2030, and therefore it will take a long period for approval for treatment in children with Angelman syndrome.

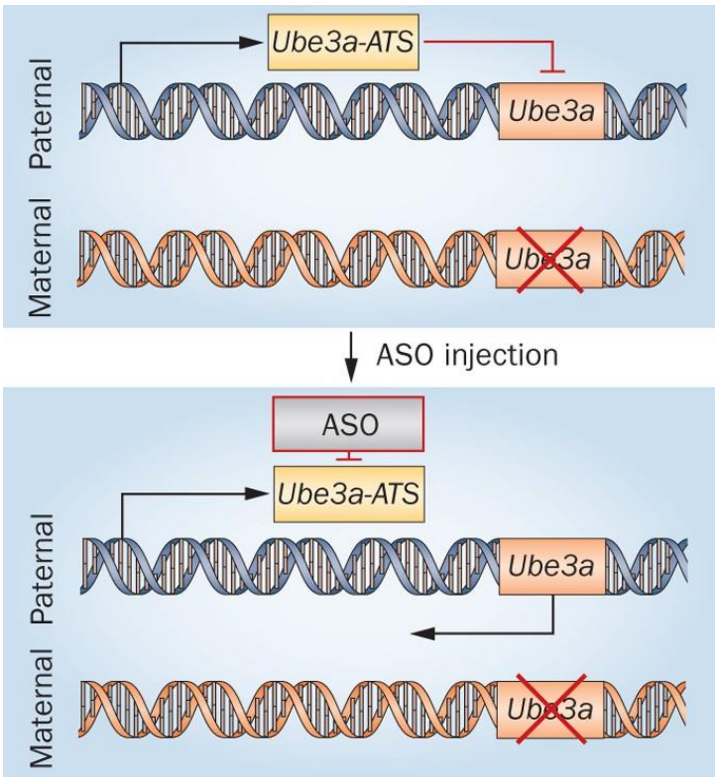

Fig. 1. Mechanism of action of antisense oligonucleotides
Source: Malkki (2015)

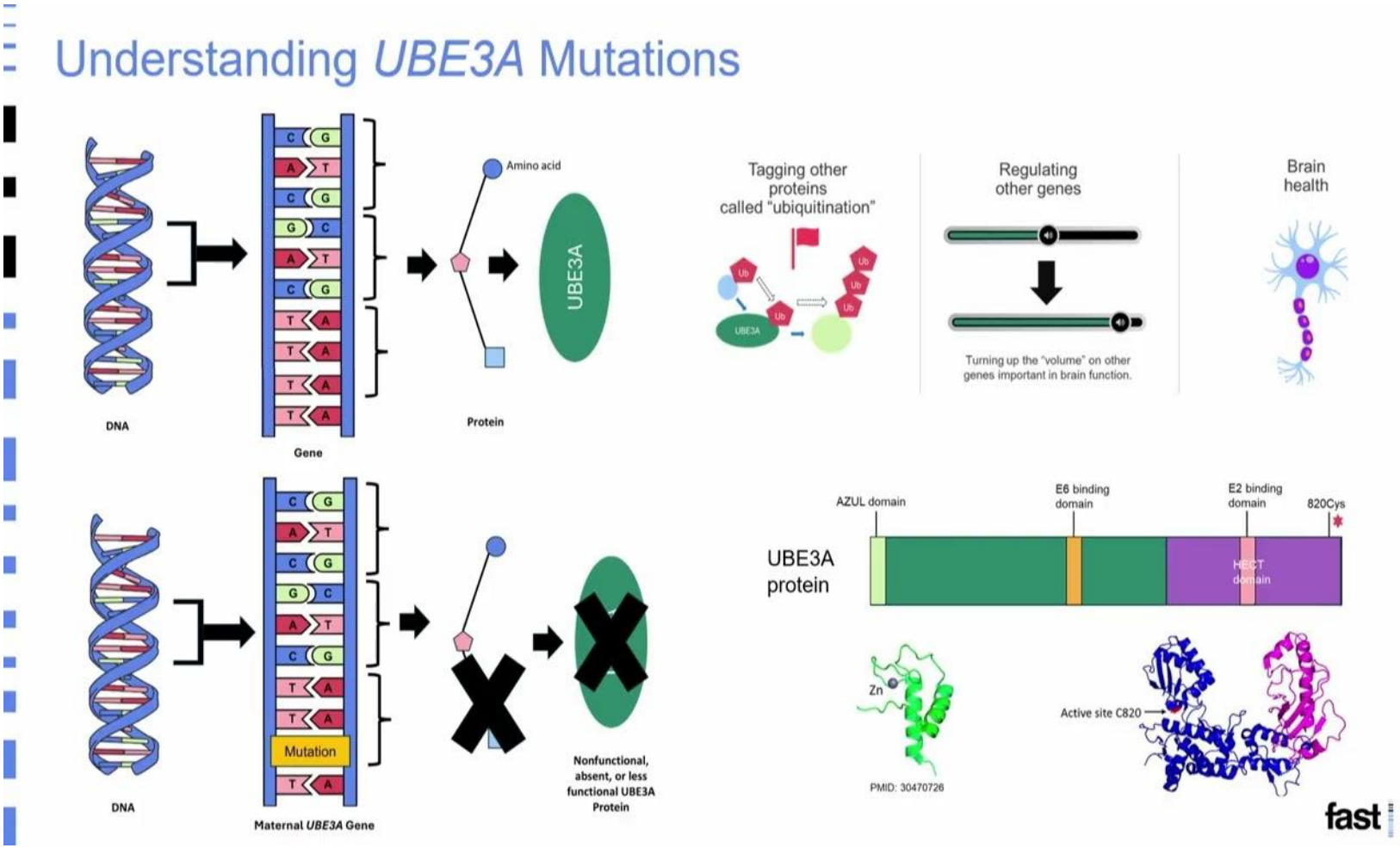

Fig. 2. *UBE3A* mutations as the origin of Angelman syndrome
Source: Armstrong (n.d.), foundation for Angelman syndrome therapeutics

5.2 CRISPR-Cas9 Technology

A CRISPR-Cas9 therapy for Angelman syndrome aims to activate the silent yet intact paternal *UBE3A* gene in the brain (Wolter et al., 2020). This is a promising disease-modifying research approach. However, successes to date have been limited to preclinical studies involving animal models and human cell cultures. Consequently, the therapy is not yet in clinical use for humans (Özlü et al., 2021; Copping et al., 2021). The biological approach is based on the neurological symptoms of Angelman syndrome that arise because the maternal *UBE3A* gene is missing or mutated. Although the paternal gene is present, it is permanently silenced in the brain by a natural RNA molecule, *UBE3A-ATS*. This is where CRISPR-Cas9 comes in. The gene scissors, Cas9, are precisely programmed to locate the regulatory sequence responsible for this silencing. By disabling this suppressor sequence, the paternal *UBE3A* gene is awakened. The goal is to enable the brain once again to produce the vital protein required for normal neuronal development.

Preclinical successes have been reached by leading research teams, including those at the University of North Carolina, which have successfully demonstrated that a single CRISPR-Cas9 injection can permanently activate the paternal gene in mice and improve behavioural symptoms. Major organisations, such as the Foundation for Angelman Syndrome Therapeutics, are investing tens of millions to further develop these gene-editing platforms and advance them to the human clinical-trial stage. The greatest hurdle lies in the safe and effective delivery of gene-editing machinery into the human brain, as well as avoiding unintended cuts elsewhere in the genome. Moreover, a one-time approach using CRISPR-Cas9 technology costs more than one million euros. Overall, this technology is at the preclinical stage, and the perspective of applying these technologies in vivo in children will require many years of future research.

6. Discussion

Angelman syndrome is a rare genetic neurobiological disorder characterised by severe intellectual and physical developmental delay, severely limited spoken language and a characteristic, exceptionally cheerful disposition (Duis et al., 2022). The disorder stems from the functional loss of the maternal *UBE3A* gene on chromosome 15. Affected individuals require ongoing support because of lifelong impairments but have a normal life expectancy. The disorder arises from absence or inactivation of the maternal copy of the *UBE3A* gene in the brain's nerve cells. The most common genetic mechanisms include maternal microdeletion. In about 70% of affected individuals, the crucial segment on the maternal chromosome 15 is missing. In paternal uniparental disomy, the child inherits two copies of chromosome 15 from the father and none from the mother. A defect may exist directly within the mother's *UBE3A* gene. Imprinting defects include a faulty epigenetic switch that should activate the gene. Pregnancy and birth usually proceed without complications. Initial developmental delays typically appear between the ages of 6 and 12 months. Typical features include pronounced cheerfulness, frequent, sometimes unprovoked, laughter and a tendency towards excitability. Almost all affected individuals develop no spoken language or only very minimal speech; however, language comprehension is significantly better developed.

Antisense oligonucleotides are currently the most widely discussed approach. The idea is to block the inhibitory *UBE3A-AS* RNA so that the paternal *UBE3A* gene is expressed again in the nervous system. Such studies are already underway or have reached clinical development. The aim of gene replacement will be to introduce functional *UBE3A* by using viral vectors. This is theoretically attractive but technically challenging in the context of the brain, as *UBE3A* levels in neurons require precise regulation; excessive expression or incorrect distribution could be problematic.

Imprinting or epigenetic editing is a highly innovative technique that involves specifically reversing silencing of the paternal copy without altering the gene itself. This could be achieved through epigenetic interventions, CRISPR-based regulatory systems or other switching mechanisms. At present, this remains largely in the realm of research rather than clinical reality. Upstream and downstream approaches may also be possible to treat specific consequences of *UBE3A* deficiency, such as synaptic dysfunction. In conclusion, the focus on curing Angelman syndrome still requires many years of detailed research, especially to develop sufficient and long-lasting efficacy, identify the correct dosage and establish the appropriate application form without producing toxic effects on brain cells. Tremendous research efforts focusing on Angelman syndrome are ongoing and may lead to more efficient, less expensive and long-lasting therapy options in the future. Overall, many of these new research efforts are in early approval stages, and it will take several years to integrate these interventional drugs into care for children with Angelman syndrome.

7. Conclusions

Angelman syndrome remains a severe lifelong neurodevelopmental disorder caused primarily by loss of functional maternal *UBE3A* expression in neurons. Current management is supportive and requires coordinated multidisciplinary care to address motor impairment, epilepsy, sleep disturbance, communication difficulties and daily functional needs. The therapeutic landscape is changing because several investigational strategies now aim to address the molecular basis of the disorder rather than only its symptoms. Antisense oligonucleotides seek to reduce *UBE3A-ATS*-mediated silencing and reactivate the paternal allele, whereas gene replacement and gene-editing approaches aim to restore *UBE3A* expression through different mechanisms. These strategies provide a rational basis for disease-modifying treatment, but they remain constrained by important uncertainties concerning delivery to the brain, dosage, timing, durability, safety and the risk of excessive or inappropriate *UBE3A* expression. Consequently, cautious interpretation is required until larger trials with longer follow-up are available. For children and families affected by Angelman syndrome, the most immediate priority remains consistent symptomatic care, while carefully conducted clinical research continues to determine whether paternal gene reactivation or gene replacement can provide safe and sustained clinical benefit. Future work should clarify genotype-specific responses and establish outcome measures that are meaningful for patients, caregivers and clinicians.

8. Limitations

This minireview is limited by its narrative design and by reliance on the published and publicly available information described in the manuscript. It does not include a systematic search strategy, formal quality appraisal, meta-analysis or grading of the strength of evidence. Several therapeutic approaches discussed, particularly antisense oligonucleotides, AAV-mediated gene replacement and CRISPR-Cas9-based strategies, remain investigational and are at different stages of preclinical or clinical development. Therefore, conclusions regarding comparative efficacy, durability of response, optimal dose, timing of intervention and long-term safety cannot be drawn. Some trial outcomes are preliminary, and follow-up periods are still insufficient to assess sustained developmental benefit or delayed adverse effects. In addition, Angelman syndrome is genetically heterogeneous, and treatment responses may vary according to deletion status, *UBE3A* mutation, imprinting defect or paternal uniparental disomy. The manuscript therefore provides an overview rather than definitive clinical guidance for therapeutic decision-making.

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

Authors have declared that no competing interests exist.

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